~~Confidential~~

Helsinki, 22 April 2022

Addressees
Registrant(s) of JS_2944-06-1_Sub as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
22 December 2020

Registered substance subject to this decision ("the Substance")
Substance name: hexadecyl hydrogen maleate
EC number: 220-942-8

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***30 October 2023***.

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. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

3. Growth inhibition study 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 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)

5. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and 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)

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

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

8. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; test method: EU C.47./OECD TG 210)

9. Simulation testing on ultimate degradation in surface water (triggered by Annex VIII, Section 9.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

10. Identification of degradation products (triggered by Annex VIII, Section 9.2; test method: using an appropriate test method or EU C.25./OECD TG 309).

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

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

Appeal

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

Failure to comply

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

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

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

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

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. Assessment of weight of evidence adaptations

0.1.1. Information provided

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

- In vitro gene mutation study in bacteria
- In vitro cytogenicity study in mammalian cells
- In vitro gene mutation study in mammalian cells
- Short-term repeated dose toxicity study (28 days)
- Screening for reproductive/developmental toxicity.

0.1.2. Assessment of the information provided

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

3 Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing the specific standard information requirements in the following appendices.

4 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.

5 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 that the Substance has or has not the (dangerous) property investigated by the required study.

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

7 You have provided separate justification documents for the weight of evidence adaptation for the information requirements In vitro cytogenicity study in mammalian cells, In vitro gene mutation study in mammalian cells, and Screening for reproductive/developmental toxicity, respectively. You provided a description of the studies without integration and weighing. For the information requirements In vitro gene mutation in bacteria and Short-term repeated dose toxicity (28 days) you have not provided a justification for the weight of evidence adaptation. You have not included a justification with an assessment, integration and weighing of the individual sources of information for relevance, reliability, consistency and results, and subsequently decided whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

8 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.

9 The issue identified below is essential for all the information requirements in which you invoked a weight of evidence.

0.1.2.1. Reliability of the read across approach

10 Section 0.2. 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.

11 The issue identified below is essential for the information requirements In vitro cytogenicity study in mammalian cells, In vitro gene mutation study in mammalian cells, and Screening for reproductive/developmental toxicity.

0.1.2.2. Reliability of the QSAR information

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

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

13 You have provided "general mechanistic" and "endpoint specific profile predictions as per QSAR Toolbox v.4.4.", and using the Danish (Q)SAR database, in your weight of evidence justification documents for two toxicological information requirements (in vitro cytogenicity study in mammalian cells, and in vitro gene mutation study in mammalian cells), and in your read-across justification document for several toxicological information requirements.

14 You do not provide an applicability domain of the model(s) (e.g. describing descriptor ranges, structural fragments covered, mechanistic and metabolic domains) nor information on the training set compounds of the model.

15 Without access to the training set of the model(s), ECHA cannot verify the applicability domain of the model and confirm that this model(s) is suitable to predict properties of the Substance.

16 Furthermore, you have not included the QPRFs in your technical dossier which would allow verification of the reliability of the model prediction within the model used.

17 Therefore, the QSAR predictions are not considered reliable, because it can not be established whether the (Q)SAR models are scientifically valid and/or that the Substance falls within the applicability domain of the prediction models.

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

0.2. Assessment of the read-across approach

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- 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.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

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

21 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.

22 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 toxicological properties

23 You provide a read-across justification document in IUCLID Section 13.

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

Source substance 1	Maleic acid, EC No. 203-742-5
Source substance 2	1-hexadecanol, EC No. 253-149-0
Source substance 3	Maleic anhydride, EC No. 203-571-6

25 Additional source substances included in separate weight of evidence documents in your dossier but not included in your main read-across justification document:

Source substance 4	1-dodecanol
Source substance 5	Octadecane-1-ol
Source substance 6	Behenyl alcohol
Source substance 7	2-ethylhexanol
Source substance 8	1-docosanol
Source substance 9	C14-16 alcohol.

26 In your read-across justification document you provide the following reasoning for the prediction of toxicological properties: ”It is hypothesised that the Target substance being an ester of maleic acid and 1-hexadecanol, will hydrolyse to its starting materials and therefore the systemic toxicity of the substance will follow the toxicological profile of these two expected hydrolysis products. The use of maleic anhydride takes into account its readily hydrolysis to maleic acid”.

27 ECHA understands that your read-across hypothesis (regarding source substances 1-3) is based on the formation of common (bio)transformation products. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

28 ECHA understands that you consider source substances 4-9 as analogue substances of source substance 2, and, although no read-across justification was provided, that your read-across hypothesis (regarding source substances 4-9) assumes that different

compounds have the same type of effects. You predict the properties of source substance 2 to be quantitatively equal to those of the source substances 4-9.

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

0.2.1.1. Read-across hypothesis contradicted by existing data

30 Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances". The Guidance on IRs and CSA, Section R.6.2.2.1.f. indicates that "it is important to provide supporting information to strengthen the rationale for the read-across". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

31 The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis must be provided and supported by scientific evidence.

32 As indicated above, your first read-across hypothesis is based on the assumption that the Substance hydrolyses to the source substances 1. and 2. In doing so, you claim that the systemic toxicity of the Substance will follow only the toxicological profile of the two expected hydrolysis products and not the systemic toxicity of the parent compounds, so we understand that this hypothesis assumes rapid hydrolysis to these source substances.

33 In your read-across justification document you have presented information on the hydrolysis of other maleic acid esters. You describe one old study (1926) in which the hydrolysis of diethyl maleate was reported to be very slow ("The enzymatic hydrolysis of diethyl maleate took place slowly and even after 24 hours, only 16 % of the ester was split"). Furthermore, you present data showing the hydrolysis of dimethylfumarate to monomethylfumarate (MMF) at pH 8 but not at pH 1. In addition, you note that "In these conditions MMF and MEF monoethylfumarate remained intact during the period of analysis (6 h)".

34 Thus, the data you presented does not show rapid hydrolysis of diethylmaleate to corresponding acid and alcohol.

35 You also provided general mechanistic" and "endpoint specific profile predictions"; QSAR Toolbox v.4.4.

36 You have not provided any experimental data on the hydrolysis of the Substance. The available set of data on maleates and fumarates, presented in your read-across justification document, contradicts your read-across hypothesis which assumes rapid hydrolysis of the substances resulting in the corresponding acid and alcohol.

37 The QSAR information is not reliable for the reasons explained above (Section 0.1.2.2). Further, regarding the use of QSARs for the identification of hydrolysis products (ii), the QSAR Toolbox provides information on the expected hydrolysis end-products. However, no information on the hydrolysis rate is obtained, which is an important parameter to be described in experimental hydrolysis studies.

38 Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

0.2.1.2. Missing supporting information/bridging data

39 Annex XI, Section 1.5 of the REACH Regulation states that "physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)". For this purpose "it is important to provide supporting information to strengthen the rationale for the read-across" (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

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

41 As indicated above, your first read-across hypothesis (related to source substances 1-3) is based on the (bio)transformation of the Substance to the source substance(s). Your second read-across hypothesis (related to source substances 4-9) assumes that different compounds have the same type of effects. In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

42 For the source substance(s), you provide studies used in the prediction in the registration dossier. Apart from those studies, your read-across justification or the registration dossier does not include any robust study summaries or descriptions of data for the Substance that would confirm that the Substance and source substances cause the same type of effects.

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

0.2.1.3. Assessment of (Q)SAR information

44 Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. The first OECD principle requires the endpoint of a (Q)SAR model to be well defined. ECHA Guidance R.6.5.1.2 specifies that for a well-defined endpoint:

i. the training set must be obtained from experimental data generated with homogeneous experimental protocols, and

ii. the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement.

45 In your read-across justification document you provided

(i) "general mechanistic" and "endpoint specific profile predictions; QSAR Toolbox v.4.4.".

(ii) In addition, in relation to your hypothesis on the hydrolysis of the Substance, you explain that "This is confirmed by the hydrolysis stimulation carried out using the structure of the substance in QSAR Toolbox 4.4. Only two hydrolysis products were identified for the substance: maleic acid and 1-hexadecanol".

46 As explained under Section 0.1.2.2., your QSAR predictions (i) are not considered reliable.

47 Furthermore, ECHA notes, regarding the use of QSARs for the identification of hydrolysis products (ii), that the QSAR Toolobox provides information on the expected hydrolysis end-products. However, no information on the hydrolysis rate is obtained, which is an important

parameter to be described in experimental hydrolysis studies. Therefore you have not demonstrated and justified your hypothesis, which assumes rapid hydrolysis of the substances resulting in the corresponding acid and alcohol.

0.2.2. Conclusion on the read-across approach

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

0.3. Triggering of long-term aquatic invertebrates and fish toxicity testing at Annexes VII and VIII

The same considerations provided below apply to the triggering of long-term aquatic toxicity studies at Annexes VII and VIII (Column 2).
Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

49 In the provided OECD TG 105 (2020), the saturation concentration of the Substance in water was determined to be 0.0907 mg/L.

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

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

51 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

52 You have adapted this information requirement by using a Weight of evidence approach under Annex XI, Section 1.2 of REACH and a Grouping of substances and read-across approach under Annex XI, Section 1.5 of REACH based on experimental data from the following substances:

(i) In vitro gene mutation study in bacteria (1988) with Maleic acid (EC 203-742-5)

(ii) In vitro gene mutation study in bacteria (1982) with Hexadecanol (EC 249-583-5).

1.2. Assessment of the information provided

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

1.2.1. Read-across adaptation rejected

54 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.

1.2.2. Weight of evidence adaptation rejected

55 As explained in Section 0.1., your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

1.2.2.1. Studies not reliable for the information requirement

56 As explained under Section 0.1., 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.

57 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Section 8.4.1. at Annex VII includes information on gene mutation in bacteria. A level of information on these aspects similar to that obtained from OECD TG 471 (2020) studies is required.

58 The sources of information (i-ii) provide relevant information on gene mutation in bacteria. However, these sources of information have the following deficiencies affecting their reliability.

59 The reliability of sources of information (i) and (ii) is significantly affected by the deficiency identified and explained under Section 0.1.

60 In addition, sources of information (i) and (ii) have the following deficiencies:

61 Testing in accordance with OECD TG 471, requires that the following specifications/conditions have to be met:

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)
b) The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 µl/plate.
c) At least 5 doses must be evaluated, in each test condition.

62 The study (i) is described as In vitro gene mutation study in bacteria. However, this study shows the following:

a) no required fifth strain included.

63 The study (ii) is described as In vitro gene mutation study in bacteria. However, this study shows the following:

a) no required fifth strain included.

b) the dose tested was 50 µg/plate without reported precipitation or observed limiting cytotoxicity.

c) only one dose was tested.

64 The information provided does not cover some of the conditions required by OECD TG 471.

65 In the absence of such information on those critical aspects of the specification/conditions of the provided studies, ECHA cannot evaluate the reliability of the conclusions on gene mutations in bacteria.

1.2.2.2. Conclusion on weight of evidence

66 In summary, the sources of information (i) and (ii) provide information on gene mutation in bacteria but have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause gene mutations in bacteria.

67 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 vitro cytotoxicity study in mammalian cells or in vitro micronucleus study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

1.3. Specification of the study design

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

2. Long-term toxicity testing on aquatic invertebrates

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

70 As already explained under Section 0.3., the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

2.1. Information provided

71 You have provided a "preliminary study of the OECD Guideline 202", but no information on long-term toxicity on aquatic invertebrates for the Substance.

2.2. Assessment of the information provided

72 We have assessed this information and identified the following issue:

73 In the absence of any information on long-term toxicity on aquatic invertebrates, the information requirement is not fulfilled.

2.3. Study design and test specifications

74 The Substance is difficult to test due to the low water solubility (0.0907 mg/L), adsorptive properties: log Kow of >6.5 and log Koc of 3.954 and based on the presence of carboxyl group the Substance potentially may be present in ionised form at environmentally relevant pHs (4-9). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. 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 211. 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 solutions.

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 provided a "preliminary study of the OECD Guideline 201" on the Substance.

3.2. Assessment of the information provided

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

3.2.1. Reliability of the study

78 To fulfil the information requirement, a study must comply with OECD TG 201 (Article 13(3) of REACH). Therefore, the following specifications must be met:

- analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;
- the test design is reported (*e.g.*, number of replicates, used controls);
- the test conditions are reported (*e.g.*, test temperature, test species, biomass

density at the beginning of the test);

- the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported;
- the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;

79 Your registration dossier provides a "preliminary study of the OECD Guideline 201" showing following:

- no analytical monitoring of exposure was conducted and no justification why the analytical monitoring of exposure concentrations is not technically feasible provided;
- on the test design, you have not specified number of replicates used for each test concentration and for control(s);
- on the test conditions, you have not specified test temperature, test species, biomass density at the beginning of the test;
- the method used to determine algal biomass is not reported;
- tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

80 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, no analytical monitoring of exposure was conducted. Furthermore, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, there is no information about number of replicates used, about test species, biomass density at the beginning of the test, tabulated data on the algal biomass determined daily for each treatment group and control(s) are not reported etc.

81 Therefore, the requirements of OECD TG 201 are not met.

3.2.2. Compliance with principles of good laboratory practice

Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.
You indicate in the registration dossier that the provided study was performed in 2020 and was not performed according to GLP.
Thus, the study does not comply with requirements of Article 13(4) of REACH.

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

3.3. Study design and test specifications

OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specification' under Section 2.3.

Reasons related to the information under Annex VIII of REACH

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

83 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.).

4.1. Information provided

84 You have adapted this information requirement by using a Weight of evidence approach under Annex XI, Section 1.2 of REACH and a Grouping of substances and read-across approach under Annex XI, Section 1.5 of REACH based on experimental data from the following substances:

(i) Brief summaries of (a) in vitro and (b) in vivo chromosomal aberration studies with maleic anhydride

(ii) Brief summary of in vivo mouse micronucleus study with 1-dodecanol

(iii) Brief summary of in vivo mouse micronucleus study with octadecane-1-ol

(iv) Brief summaries of (a) in vitro chromosomal aberration study and (b) in vivo micronucleus study with behenyl alcohol.

85 Furthermore you provided "general mechanistic" and "endpoint specific profile predictions as per QSAR Toolbox v.4.4." in support of your read-across adaptation.

4.2. Assessment of the information provided

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

4.2.1. Read-across adaptation rejected

87 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.

4.2.2. Weight of evidence adaptation rejected

88 As explained in Section 0.1., your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

4.2.2.1. Studies not reliable for the information requirement

89 As explained under Section 0.1., 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.

90 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII includes: detection and quantification of cytotoxicity and the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei in cultured mammalian cells (in vitro) or in mammals (in vivo).

91 A level of information on these aspects similar to that obtained from in vitro/in vivo chromosomal aberration tests (OECD TG 473/OECD TG 475) or in vitro/in vivo micronucleus tests (OECD TG 487/OECD TG 474) is required.

92 The sources of information (i-iv) provide relevant information on detection and quantification of cytotoxicity and the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei. However, these sources of information have the following deficiencies affecting their reliability.

93 The reliability of sources of information (i-iv) is significantly affected by the deficiencies identified and explained under Section 0.1.

94 In addition, the sources of information (i.a and iv.a) have the following deficiencies:

95 Testing in accordance with OECD TG 473[2], requires that the following specifications/conditions have to be met:

a) Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation.
b) 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.
c) At least 3 concentrations must be evaluated, in each test condition.
d) At least 300 well-spread metaphases must be scored per concentration.
e) 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.
f) Data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures must be reported.

96 The study (i.a) is described as in vitro chromosomal aberration study. However, this study shows the following:

a) No information on two separate test conditions (absence and presence of metabolic activation)
b) No information on doses tested.
c) No information on number of test concentrations.
d) Scoring of only 100 metaphases per concentration.
e) No information on a positive control.
f) No quantitative data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures.

97 The study (iv.a) is described as in vitro chromosomal aberration study. However, this study shows the following:

a) No information on cytotoxicity or justification for the selection of the doses.
b) Scoring of only 100 metaphases per concentration.
c) No information on a positive control.
d) No quantitative data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures.

98 The source of information (i.b) has the following deficiencies:

99 Testing in accordance with OECD TG 475, requires that the following specifications/conditions have to be met:

[2] ECHA Guidance R.7a, Table R.7.7–2, p.557

a) The study must include a minimum of three doses/groups of treated animals as well as a negative control group and a positive control group.
b) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that is tolerated without evidence of toxicity (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia). The highest dose can also be a dose that produces toxicity in the bone marrow.
c) The mitotic index must be determined as a measure of cytotoxicity in at least 1000 cells per animal for all treated animals (including positive controls), untreated or vehicle/solvent negative control animals.
d) At least 200 metaphases must be analysed for each animal for structural chromosomal aberrations including and excluding gaps.
e) The mitotic index and the mean number of cells with aberrations per group must be reported for each group of animals.

100 The study (i.b) is described as in vivo chromosomal aberration study. However, this study shows the following:

a) Only two doses were tested and no information on positive control group was provided.
b) No justification for the dose selection.
c) No data on the data on the mitotic index and the mean number of cells with aberrations per group for each group of animals.

101 The sources of information (ii, iii and iv.b) have the following deficiencies:

102 Testing in accordance with OECD TG 474, requires that the following specifications/conditions have to be met:

f) The study must include a minimum of three doses/groups of treated animals as well as a negative control group and a positive control group.
g) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that is tolerated without evidence of toxicity (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia). The highest dose can also be a dose that produces toxicity in the bone marrow (e.g. a reduction in the proportion of immature erythrocytes among total erythrocytes in the bone marrow or peripheral blood).
h) The proportion of immature among total (immature + mature) erythrocytes must be determined for each animal (by counting a total of at least 500 erythrocytes for bone marrow and 2000 erythrocytes for peripheral blood).
i) At least 4000 immature erythrocytes per animal must be scored for the incidence of micronucleated immature erythrocytes.
j) The proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes must be reported for each group of animals.

103 The study (ii) is described as in vivo micronucleus test. However, this study shows the following:

a) Only one dose was tested.
b) No data presented on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals.

104 The study (iii) is described as in vivo micronucleus test. However, this study shows the following:

a) No justification for the dose selection.
b) No data presented on the proportion of immature erythrocytes among total

erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals.

105 The study (iv.b) is described as in vivo micronucleus test. However, this study shows the following:

a) No data presented on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals.

106 In the absence of information on the critical aspects of the specification/conditions of the provided studies, ECHA cannot evaluate the reliability of the conclusions on cytotoxicity and the frequency of cells with structural chromosomal aberration(s).

4.2.2.2. Conclusion on weight of evidence

107 In summary, the sources of information (i-iv) provide information on cytotoxicity and the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei in cultured mammalian cells but have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause cytotoxicity and the quantification of the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei.

108 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 in vitro cytotoxicity study in mammalian cells or in vitro micronucleus study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

4.3. Specification of the study design

109 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.

5. In vitro gene mutation study in mammalian cells

110 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.

111 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.

112 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 sections 1 and 4.

113 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.

114 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 provides a negative result.

5.1. Information provided

115 You have adapted this information requirement by using a Weight of evidence approach under Annex XI, Section 1.2 of REACH and a Grouping of substances and read-across approach under Annex XI, Section 1.5 of REACH based on experimental data from the following substances:

(i) Brief summaries of in vitro gene mutation studies (i.a and i.b) with maleic acid

(ii) Brief summaries of in vitro gene mutation studies (ii.a and ii.b)with 2-etylhexanol

(iii) Brief summary of in vitro gene mutation study with behenyl alcohol

116 Furthermore you provided predictions using the Danish (Q)SAR Database in support of your read-across adaptation.

5.2. Assessment of the information provided

117 We have assessed this information and identified the following issue:

5.2.1. Read-across adaptation rejected

118 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. Weight of evidence adaptation rejected

119 As explained in Section 0.1., your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

5.2.2.1. Studies not reliable for the information requirement

120 As explained under Section 0.1., 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.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII includes: similar information that is produced by the OECD TG 476/490 and OECD TG 488. This includes detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (*in vitro*) or mutant frequency for each tissue in mammals (*in vivo*).

121 A level of information on these aspects similar to that obtained from 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) is required.

122 The sources of information (i-iii) provide relevant information on detection and quantification of gene mutations including data on the frequency of mutant colonies in cultured mammalian cells (in vitro). However, these sources of information have the following deficiencies affecting their reliability.

123 The reliability of sources of information (i-iii) is significantly affected by the deficiency identified and explained under Section 0.1.

124 In addition, the sources of information (i-iii) have the following deficiencies:

125 Testing in accordance with OECD TG 476[3], requires that the following specifications/conditions have to be met:

a) Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

126 The studies (i-iii) are described as in gene mutation studies. However, these studies show the following:

a) No quantitative data on the cytotoxicity and the mutation frequency for the treated and control cultures.

127 In the absence of information on the critical aspects of the specification/conditions of the provided studies, ECHA cannot evaluate the reliability of the conclusions on gene mutation in mammalian cells.

5.2.2.2. Conclusion on weight of evidence

128 In summary, the sources of information (i-iii) provide information on gene mutation in mammalian cells but have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause gene mutations in mammalian cells.

129 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 in vitro gene mutation studies in mammalian cells. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

5.3. Specification of the study design

130 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.

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

131 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.).

6.1. Information provided

132 You have adapted this information requirement by using a Weight of evidence approach under Annex XI, Section 1.2 of REACH and a Grouping of substances and read-across approach under Annex XI, Section 1.5 of REACH based on experimental data from the following substances:

(i) 2-year feeding study (1947) with Maleic acid (EC 203-742-5)

(ii) 13-week feeding study (1966) with Hexadecanol (EC 253-149-0)

(iii) 2-year feeding study (1983) with Maleic anhydride (EC 203-571-6).

[3] ECHA Guidance R.7a, Table R.7.7–2, p.557

6.2. Assessment of the information provided

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

6.2.1. Read-across adaptation rejected

134 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

6.2.2. Weight of evidence rejected

135 As explained in Section 0.1., your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

136 The sources of information (i-iii) provide relevant information on detection and quantification of gene mutations including data on the frequency of mutant colonies in cultured mammalian cells (in vitro). However, these sources of information have the following deficiencies affecting their reliability.

6.2.2.1. Source study not reliable

137 You have flagged study (i) as unassignable/unreliable, which ECHA agrees with.

6.2.2.2. Source studies not reliable for the information requirement

138 As explained under Section 0.1., 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.

139 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 or TG 422. At general level, it includes information on systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity.

140 The studies (ii-iii) provide relevant information on systemic toxicity. However, these sources of information have the following deficiency affecting their reliability.

141 The reliability of the sources of information (ii-iii) is significantly affected by the deficiency identified and explained under Section 0.1.2.1.

142 Therefore, ECHA cannot evaluate the reliability of the conclusions on repeated dose toxicity.

6.2.2.3. Conclusion on weight of evidence

143 In summary, the sources of information (i-iii) provide relevant information but have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause repeated dose toxicity effects.

144 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 short-term repeated dose toxicity (28 days) studies. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

6.3. Specification of the study design

145 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.).

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

7. Screening for reproductive/developmental toxicity

147 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII to REACH (Section 8.7.1.), if there is no evidence from analogue substances, QSAR or in vitro methods that the substance may be a developmental toxicant.

7.1. Information provided

148 You have adapted this information requirement by using a Weight of evidence approach under Annex XI, Section 1.2 of REACH and a Grouping of substances and read-across approach under Annex XI, Section 1.5 of REACH based on experimental data from the following substances:

(i) Multigeneration study (1986) with Maleic anhydride (EC 203-571-6).

(ii) Short summary of a 13-week repeated dose study (1966) with 1-hexadecanol (EC 253-149-0).

(iii) Short summary of a combined repeated dose and reproductive/developmental toxicity study (1992) with 1-dodecanol (CAS 112-53-8).

(iv) Short summary of a combined repeated dose and reproductive/developmental toxicity study (1992) with 1-octadecanol (CAS 112-92-5).

(v) Short summary of a reproductive toxicity study (2002) with 1-docosanol (CAS 661-19-8).

(vi) Short summary of a 90-day repeated dose toxicity study (1978) with C14-16 alcohol.

7.2. Assessment of the information provided

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

7.2.1. Read-across adaptation rejected

150 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.

7.2.2. Weight of evidence rejected

151 As explained in Section 0.1., your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

7.2.2.1. Studies not adequate for the information requirement

152 As explained under Section 0.1., 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.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex VIII includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

153 A level of information on these aspects similar to that obtained from screening for reproductive/developmental toxicity studies (OECD TG 421/422) is required.

154 The studies (i-vi) provide relevant information on sexual function and fertility, toxicity to offspring, and systemic toxicity. However, these sources of information have the following deficiencies affecting their reliability.

155 The reliability of all sources of information (i-vi) is significantly affected by the deficiency identified and explained under Section 0.1.2.1.

156 In addition, the sources of information (ii-vi) have the following deficiencies:

157 (Eco)toxicological studies must comply with a recognised test method (Art. 13(3) of REACH), in this case EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Such study must cover the key parameters of the corresponding OECD test guideline (Art. 13(3) of REACH). Therefore, the following specifications must be met:

a. an exposure duration of at least four weeks for males, including a minimum of two weeks prior to mating, and approximately 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation;

b. examination of parameters for sexual function and fertility such as mating and fertility, duration of gestation and parturition and weight and histopathology of reproductive organs and tissues;

c. examination of offspring parameters such as number and sex of pups, stillbirths and live births, gross abnormalities, litter weight, anogenital distance, and number of nipples and areolae in male pups.

158 The sources of information (ii-vi) are very briefly described only in the weight of evidence justification document, without details on exposure duration, examination of parameters for sexual function and fertility, and examination of offspring parameters. Therefore it is not possible to assess the reliability of the data.

159 In the absence of information on the critical aspects of the specification/conditions of the provided studies, ECHA cannot evaluate the reliability of the conclusions on reproductive/developmental toxicity.

7.2.2.2. Conclusion on weight of evidence

160 In summary, the sources of information (i-vi) have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause reproductive/developmental toxicity.

161 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 screening for reproductive/developmental toxicity study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

7.3. Specification of the study design

162 A study according to the test method EU B.64/OECD TG 422 must be performed in rats.

163 The study must be conducted with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

164 Therefore, the study must be conducted in rats with oral administration of the Substance.

8. Long-term toxicity testing on fish

165 Short-term toxicity testing on fish is an information requirement under Column 1 of Annex VIII to REACH (Section 9.1.3.). However, long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

8.1. As already explained under Section 0.3., the Substance is poorly water soluble and information on long-term toxicity on fish must be provided. Information provided

166 You have provided a "preliminary study of the OECD Guideline 203", but no information on long-term toxicity on fish for the Substance.

8.2. Assessment of the information provided

167 We have assessed this information and identified the following issue:

168 In the absence of any information on long-term toxicity on fish, the information requirement is not fulfilled.

8.3. Study design and test specifications

169 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.).

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 specification' under Section 2.3.

9. Simulation testing on ultimate degradation in surface water

170 Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

171 This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (Guidance on IRs and CSA, Section R.11.4.). This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP) as:

  - it is not readily biodegradable (*i.e.* <60/70% degradation in an OECD 301B)
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as:
  - it has a high potential to partition to lipid storage (*e.g.* log K_{ow} > 4.5);
  - it has a high potential for bioaccumulation in air-breathing organisms (log K_{ow} >2 and log K_{oa} >5);
  - for some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes) and high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipid.

172 Your registration dossier provides the following:

- The Substance is not readily biodegradable (17% degradation after 28 days in OECD TG 301B);
- The Substance has a high potential to partition to lipid storage (Log K_{ow} of >6.5 based on OECD TG 117);
- The Substance has a high potential for bioaccumulation in air-breathing organisms(Log K_{ow} of >6.5 based on OECD TG 117 and log K_{oa} of 14.197 based on the estimation by KOAWIN v1.10 model;
- Based on the presence of carboxyl group the Substance potentially may be present in ionised form at environmentally relevant pHs (4-9) and may be surface active due to the presence of hydrophobic carbon chain and hydrophylic (potentially ionised) carboxylic acid group, i.e. may be capable of reducing the surface tension of water. Therefore, high potential for bioaccumulation of the Substance cannot be excluded based on available information.

173 Furthermore, the information in your dossier is currently incomplete and therefore:

- it is not possible to conclude on the toxicity of the Substance see Sections 2, 3 and 8 of this decision).

174 Based on the above, the available information on the Substance indicates that it is a potential PBT/vPvB substance.

175 Under section 2.3 of your IUCLID dossier and section 8 of your chemical safety report ('PBT assessment'), you conclude that the Substance is not B/vB. In support of your conclusion you provide the following additional information: "The substance has a LogKow higher than 6.5. However, the predicted BCF of the substance (10 l/kg) suggests that the BCF of the substance is much lower than BCF threshold value for bioaccumulation (2000 l/kg). Thus the substance is not considered to be B or vB.".

176 We have assessed the information provided and identified the following issues.

9.1. Lack of documentation of the model

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

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

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

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

179 However, in support of predicted bioconcentration factor (BCF) you have not provided adequate and reliable documentation. In absence of such information, ECHA cannot establish that the prediction can be used for the purpose of PBT/vPvB assessment.

9.2. Use of QSAR predictions to reach definite conclusion on B/vB

180 Pursuant to Section 3.2.2 of Annex XIII B and vB properties are concluded on the basis of:

a) Results from a bioconcentration or bioaccumulation study in aquatic species;
b) Other information on the bioaccumulation potential provided that its suitability and reliability can be reasonably demonstrated, such as:
   - Results from a bioaccumulation study in terrestrial species;
   - Data from scientific analysis of human body fluids or tissues, such as blood, milk, or fat;
   - Detection of elevated levels in biota, in particular in endangered species or in vulnerable populations, compared to levels in their surrounding environment;
   - Results from a chronic toxicity study on animals;
   - Assessment of the toxicokinetic behaviour of the substance;
c) Information on the ability of the substance to biomagnify in the food chain, where possible expressed by biomagnification factors or trophic magnification factors.

181 In the section R.11.4.1.2.10 of ECHA Guidance R.11 it is explained that data generated by application of QSAR models can be used in a Weight-of-Evidence approach for the B and vB assessment, i.e. together with other lines of evidence relevant and reliable for the assessment of bioaccumulation potential of a substance. Therefore, QSAR on its own does not qualify as suitable information to conclude on B/vB properties.

182 You have provided exclusively a QSAR to reject the conclusion of potential B/vB based on the screening information (Log Kow and other information listed above).

183 This information on its own, however, is insufficient to conclude on B or vB property and/or to remove the concern raised by the screening information.

184 Therefore, the additional information from your PBT assessment is not adequate to conclude that the Substance is not a potential PBT/vPvB substance.

185 Further, the additional information from your PBT assessment is not adequate to conclude on the PBT/vPvB properties of the Substance.

186 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

9.3. Information provided

187 There is no information on simulation testing on ultimate degradation in surface water provided in the registration dossier.

9.4. Assessment of the information provided

188 We have assessed the information provided and identified the following issues.

189 In the absence of information on simulation testing on ultimate degradation in surface water, the information requirement is not fulfilled.

9.5. Study design and test specifications

190 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

191 You must perform the test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (Guidance on IRs and CSA, Section R.11.4.1.1.3.).

192 The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (Guidance on IRs and CSA, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 309.

193 As specified in Guidance on IRs and CSA, Section R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test material concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (Guidance on IRs and CSA, Section R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

194 Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 309; Guidance on IRs and CSA, Section R.11.4.1.).

10. Identification of degradation products

195 Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

196 As already explained under Section 9., the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

10.1. Information provided

There is no information on identity of degradation products provided in the registration dossier.

10.2. Assessment of the information provided

197 We have assessed the information provided and identified the following issues.

198 In the absence of information on identity of degradation products, the information requirement is not fulfilled.

10.3. Study design and test specifications

199 Regarding the selection of appropriate and suitable test method(s), the method(s) will have to be substance-specific. Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You may obtain this information from the degradation study requested in Section 9 of this Appendix or by some other measure. If any other method is used for the identification of the transformation/degradation products, you must provide a scientifically valid justification for the chosen method.

200 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Section 9 of this Appendix) must be conducted at 12°C and at a test concentration < 100 µg/L. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, e.g. 20°C) and at higher application rate (i.e. > 100 µg/L).

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 04 May 2021.

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

ECHA did not receive any comments within the commenting period.

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

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

Appendix 3: 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]

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[4].

1.2. Test material

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals