~~Confidential~~

Helsinki, 11 October 2023

Addressee
Registrant of JS_DUP-EC 222-884-9 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
29/06/2021

Registered substance subject to this decision ("the Substance")
Substance name: diundecyl phthalate
EC number/List number: 222-884-9

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 under request 4 below by ***18 October 2024*** and all other information by ***19 October 2026***.

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

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

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test OECD TG 471 (2020)) using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102

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 on 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. A/B/C/D/E/F/OECD TG 301A/B/C/D/E/F or EU C.29./OECD TG 310)

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

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

6. Justification for an adaptation of the short-term repeated dose toxicity study (28 days) (Annex VIII, Section 8.6.1., Column 2) based on the request 8 below,

   or in case the sub-chronic toxicity study (90 days) is not requested,

   Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.) by oral route, in rats

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

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

8. Sub-chronic toxicity study (90 days), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats

9. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

The reasons for the requests are explained in Appendix 1.

Information required depends on your tonnage band

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

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

Appendix 1: Reasons for the requests
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 requests

Contents

Reasons common to several requests

0.1. Read-across adaptation rejected

1 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* micronucleus study (Annex VIII, Section 8.4.2.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)

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

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

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

0.1.1. Scope of the grouping of substances (category)

5 You provide read-across justification documents in IUCLID Section 7.

6 For the purpose of this decision, the following abbreviations are used for the substances that ECHA understood are the category members, based on the information provided in the current dossier:

- DTP, di(tridecyl) phthalate, EC 204-294-3,
- DINP, diisononyl phthalate, EC 271-090-9;
- DIDP, diisodecyl phthalate, EC 271-091-4;
- D911P, 1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, EC 271-085-1

7 However, in the Category of High Molecular Weight Phthalate Esters (HMWPE) document, which you provided as part of your comments to the draft decision, you clarify that it is the following seven substances that are included in the HMWPE category:

- Di-phC10 PE, 1,2-Benzenedicarboxylic acid, 1,2-bis(2-propylheptyl) ester, EC 258-469-4,
- Di-C7-9 PE, 1,2-Benzenedicarboxylic acid, di-C7-9-branched and linear alkyl esters, EC 271-083-0
- Di-C11 PE, 1,2-benzenedicarboxylic acid, di-C11-branched and linear alkyl esters, EC 287-401-6
- Di-C9-11 PE, 1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, EC 271-085-1
- Di-C11 PE, 1,2-Benzenedicarboxylic acid, diundecyl ester, EC 222-884-9

- Di-C13 PE, 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich, EC 271-089-3
- Di-C13 PE, 1,2-benzenedicarboxylic acid, di-C13-alkyl ester, EC 204-294-3

8 You justify the grouping of the substances as: "The target substance belongs to the OECD HPV category High Molecular Weight Phthalate Ester (HMWPE) which consists of esters with an alkyl carbon backbone with 7 carbon (C) atoms or greater. The category is formed on the principle that substances of similar structure have similar environmental and toxicological properties". You state that the source substances D911P and DTP are members of the HMWPE category. Regarding DIDP and DINP, you specify that they are "not formally part of this category as it had been assessed previously but satisfies the category definition as its backbone length is C7 or above, and produce little, if any, effects of developmental or reproductive toxicity". As such, ECHA understands that you consider all source substances listed above (D911P, DTP, DINP and DIDP) as category members, resulting in a total of 12 category members (including the Substance).

9 In the HMWPE category document provided in your comments to the draft decision, you reiterate the chemical similarities between the substances, and state the chemical reactions through which they may be produced.

10 You define the applicability domain as:

- *"contain linear and/or branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl, didodecyl, and/or ditridecyl PEs"*
- *"The branched alkyl chains are composed of varying mixed isomers"*
- *"The length of the alkyl chains varies by substance, but the total carbon number of the longest linear C-chain (or backbone chain) is predominantly C7 or greater.*
- *"For the seven substances in the category described in this submission, the backbones range from C7 to C12"*
- Chemical similarity, similar vapour pressure, similar water solubility, and similar molecular weight
- *"…belong to the OECD HPV category High Molecular Weight Phthalate Ester (HMWPE)"*

11 In order to meet the information requirements for the Substance, ECHA understands that you rely on the sub-category of "*high molecular weight phthalates*" which include substances with side chains ranging from C7 to 13. The side chain may be linear, branched, a benzyl group or a combination of those.

12 We have identified the following issues with the proposed scope of the grouping:

0.1.1.1. Incomplete characterisation of the group members

13 Annex XI, Section 1.5 provides that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group*".

14 According to the Guidance on IRs and CSA, Section R.6, "*in identifying a category, it is important that all potential category members are described as comprehensively as possible*", because the purity profile and composition can influence the overall toxicity/properties of the potential category members (Guidance on IRs and CSA, Section R.6.2.4.1.). Therefore, qualitative and quantitative information on the compositions of the category members must be provided to confirm the category membership.

15 Furthermore, the provided information for categories consisting of UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substances needs to include qualitative compositional information of the individual constituents of the category members; as well as quantitative characterisation in the form of information on the concentration of the individual constituents of these substances; to the extent that this is measurable (Guidance on IRs and CSA, Section R.6.2.5.5.).

16 In addition, 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 MCS, UVCB or mixture, 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 the distribution of alkyl chain length and information on the branching of alkyl side carbon chain (i.e., isomeric composition) depending on the type of UVCB substance.

17 Your definition of the applicability domain of the category can be summarised as: "…*esters with an alkyl carbon backbone with 7 carbon (C) atoms or greater*. … *1,2-benzenedicarboxylic acid reacted with branched and/or linear alkyl alcohols, which are referred to as the alkyl chains in the phthalate ester molecule*."

18 Your read-across justification document contains limited compositional information for the members of your category. You provide a characterization of the Substance as a mono-constituent substance, describing the purity and composition. However, you do not report whether the other category members are mono-constituents, multi-constituents or UVCBs. You state that there are "*no relevant impurities*", but you do not specify the identity of any potentially present constituents or impurities, nor do you specify their amount.

19 You have provided no detailed information on the carbon chain length distribution and the isomeric composition of branched constituents for the Substance and the selected category members.

20 In the comments on the draft decision, you reiterate information already available and in addition provide the following information on the characterisation of several category members:

- EC 258-469-4: "*propyl branched [100% branched]*"
- EC 271-083-0: "*branched and linear [>80% linear]*"
- EC 287-401-6: "*branched, essentially methyl, and linear*"
- EC 271-085-1: "*branched and linear [>80% linear]*"
- EC 222-884-9: "*branched*"
- EC 271-089-3: "*branched, essentially methyl*"
- EC 204-294-3: "*branched*"

21 However, taking into account the information in your dossier and the additional information from your comments, you still fail to provide the following qualitative and quantitative key information for all the category listed under '0.1.1. Scope of the grouping of substances (category)':

- composition (including all impurities and/or constituents)
- whether the category members are mono-constituents, multi-constituents or UVCBs
- carbon chain length distribution and the isomeric composition of branched constituents for the Substance and the selected category members

22 Without qualitative and quantitative information on the compositions of the Substance and of the source substances, it is not possible to assess whether the attempted predictions are compromised by the composition of the source substances and to confirm that these substances fall into the definition of the category as defined by you.

0.1.2. Predictions for toxicological properties

23 You predict the properties of the Substance from information obtained from the following source substances which are used in the information requirements listed in the Section 0.1. above:

- DTP, Di(tridecyl) phthalate, EC 204-294-3,
- DINP, diisononyl phthalate, EC 271-090-9;
- DIDP, diisodecyl phthalate, EC 271-091-4;

24 You provide the following reasoning for the prediction of toxicological properties:

- "*For PEs, the critical toxicological effects are development and reproduction. These aspects are very structure dependent and are associated with molecules with a 4 to 6 carbon backbone. By contrast, PEs with 7 or more backbone carbons produce no detectable effects in reproduction and no adverse effects on development. From a very large toxicology database for phthalate esters, a structure activity can be demonstrated that best relates to the linear portion of the phthalate ester, rather than total carbon number*".
- You refer to the QSAR toolbox and in turn provide a list of profilers which you compare between the source substances and the Substance.
- For several of the category members (DTP, DINP, D911P and DIDP) you provide data matrices with study results (including physicochemical and mammalian toxicity) and perform a pairwise comparison to the Substance.

25 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substances.

26 In the comments to the draft decision, you reiterate the reasoning provided above. In your HMWPE document, you elaborate that "*the substance without data as well as the substance(s) with data are similar such that their physicochemical, biological, and toxicological properties would be expected to behave in a predictably similar manner or logically progress across a defined range*" and "*the substance without data possesses small incremental structural differences from the reference substance(s) or the difference between the two will not affect the property sufficiently that it cannot be accurately predicted.*"

27 We have identified the following issues with the predictions of toxicological properties:

0.1.2.1. Insufficient data density

28 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".

29 According to the Guidance on IRs and CSA, Section R.6.2.1.5., one of the factors in determining the robustness of a category is the density and distribution of the available data across the category. To identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information

covering the range of structural variations identified among the category members needs to be available.

30 Furthermore, in larger categories there may be breaks in trends which could affect the reliability of interpolation (Guidance on IRs and CSA, Section R.6.2.2.2.). To confirm that there are no such breakpoints, adequate and reliable information needs to also cover substances within a range of homologous series.

31 You have provided:

- *Two in vitro* gene mutation studies in bacteria with two category members (the Substance and EC 204-294-3)
- An in vitro mammalian chromosomal aberration test with one category member (EC 271-090-9) and two *in vivo* mammalian erythrocyte micronucleus tests with two category members (EC 271-090-9 and EC 271-091-4);
- Four sub-chronic toxicity studies with two category members (EC 271-090-9 and EC 271-091-4)

32 Information for two or three category members is not sufficient to establish a trend across the category as identified in your dossier and in your comment to the draft decision. Furthermore, in the absence of toxicity data, on the information requirements listed above, for substances between clearly defined upper and lower borders of the category, it cannot be confirmed that there is no breakpoint in toxicity trend within the given range. Therefore, the information provided is not sufficient to conclude that toxicological properties are likely to follow a regular pattern.

33 In the Category of High Molecular Weight Phthalate Esters (HMWPE) document, which you provided as part of your comments to the draft decision, you include a data matrix with poorly detailed study outcomes. Within the data matrix, in order to demonstrate a trend for the standard information requirements listed under 0.1, you list additional studies with the following substances:

- *In vitro* gene mutation study in bacteria: you claim that Di-C11 PE (CAS RN 3648-20-2), Di-C13 PE (CAS RN 68515-47-9), and Di-C13 PE (CAS RN 119-06-2) are not mutagenic. In the data matrix, you have indicated "*read-across*" in the columns of group members Di-phC10 PE (CAS RN 53306-54-0), Di-C11 PE (CAS RN 85507-79-5), and Di-C9-11 PE (CAS RN 68515-43-5). With this, ECHA understands there is no data generated with these latter three substances.
- In vitro cytogenicity study in mammalian cells: you claim that Di-C13 PE (CAS RN 119-06-2) is not mutagenic. In the data matrix you have indicated "read-across" in the columns of group members Di-phC10 PE (CAS RN 53306-54-0) and Di-C11 PE (CAS RN 3648-20-2). With this, ECHA understands there is no data generated with these latter two substances.
- Sub-chronic toxicity study (90-day) in rats, oral/dermal/inhalation: you list a single NOEL of 19.28 mg/kg bw/day in the column of Di-C11 PE (CAS RN 3648-20-2), which you have indicated as "*read-across*". With this, ECHA understands there is no data generated with this substance.

34 In summary, taking into consideration your comments on the draft decision, the data density is increased up to a cumulative total of two to five members in a category comprising 12 substances. This is only a marginal relative increase in data density, which is still insufficient to conclude that toxicological properties are likely to follow a regular pattern. Furthermore, you have not provided robust study summaries of the studies listed in your data matrix, which are required for ECHA to determine the reliability and relevance of the studies.

0.1.2.2. Missing supporting information to compare properties of the substances

35 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6., Section R.6.2.2.1.f.).

36 Supporting information must include toxicokinetic information on similar properties and supporting information or bridging studies to compare properties of the source substances information to confirm your claimed information on the impact of exposure parent compounds on the prediction.

37 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the substance(s) is necessary to confirm that the 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).

38 You have not provided any discussion nor evidence to support that toxicokinetic differences or similarities of the group members may affect the prediction of toxicity.

39 In your comments to the draft decision, you state "*Data are not specifically available on the toxicokinetics, metabolism, or distribution of the HMWPE covered under this category. However, data developed for DINP are considered to be representative, in a qualitative point of view, of other HMWPE*." However, this statement further underlines the possibility that the impact of toxicokinetic differences on your prediction cannot be excluded.

40 As part of your weight of evidence adaptation, you provide repeated-dose toxicity studies with the source substances DIDP, DINP and the Substance (request 6). In the data matrices (shown in the read-across justification documents), you list a developmental toxicity study with the Substance and developmental toxicity studies with the source substances DIDP and DINP. However, your read-across justification or the registration dossier does not include any robust study summaries for the referred developmental DIDP and DINP studies that would confirm that different substances cause the same type of effects.

41 Specific reasons why the study cannot be considered reliable are explained further below under the relevant information requirement section 6. Thus the data set reported in the technical dossier does not include relevant, reliable and adequate information for the source substances to support your read-across hypothesis.

42 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 scientifically justify the read-across.

43 In the Category of High Molecular Weight Phthalate Esters (HMWPE) document, which you provided as part of your comments to the draft decision, you include a data matrix with poorly detailed study outcomes. ECHA understands this is in an effort to provide supporting data, obtained with various group members for a wide range of standard information requirements. However, you do not include any robust study summaries for any of the referred studies. Consequently, ECHA cannot assess whether the listed studies

can be considered relevant and reliable supporting (bridging) data. To conclude, the information pertained within the data matrix is not sufficient to support your prediction for toxicological effects.

0.1.2.3. Inadequate or unreliable studies on the source substances

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

(2) be adequate for the purpose of classification and labelling and/or risk assessment;

(3) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;

(4) cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

45 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement sections 8. Therefore, no reliable predictions can be made for these information requirements.

0.1.3. Conclusion on the read-across approach

46 Based on the 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.

0.2. Weight of evidence adaptation rejected

47 You have adapted the following standard information requirements by using Annex XI, Section 1.2. (weight of evidence):

- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

48 Additionally in your comments to the draft decision, you indicate your intention to adapt the standard information requirement on ready biodegradability (Annex VII, Section 9.2.1.1) by using a weight of evidence adaptation.

49 Your weight of evidence adaptation raises the same decifiency 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.

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

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

52 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of

results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude on the corresponding information requirement.

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

54 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.

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

0.2.1. Endpoint-specific issues

56 Your weight of evidence approach has deficiencies that are specific for these information requirements individually. The specific deficiencies are set out under the information requirement concerned in the Appendices below.

Reasons related to the information under Annex VII of REACH

1. *In vitro* gene mutation study in bacteria

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

1.1. Information provided

58 You have provided:

(i) an *in vitro* gene mutation study in bacteria (1985) with the Substance;

(ii) an *in vitro* gene mutation study in bacteria (1986) with the source substance di(tridecyl) phthalate, EC 204-294-3.

1.2. Assessment of the information provided

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

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

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

60 In study(i):

a) the test was performed with the strains TA1535, TA1537, TA98 and TA100 (i.e., the strain *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is missing);

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

62 Therefore, the information requirement is not fulfilled.

1.2.1. Read-across adaptation rejected

63 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.

1.3. Specification of the study design

64 To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471, 2020) should be performed using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102.

2. Short-term toxicity testing on aquatic invertebrates

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

2.1. Information provided

66 You have provided a short-term toxicity study on *Daphnia magna* (1995) with the Substance.

2.2. Assessment of the information provided

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

67 To fulfil the information requirement, a study must comply with OECD TG 202 and the specifications of OECD GD 23 if the substance is difficult to test(Article 13(3) of REACH). Based on all information available on the Substance, in particular water solubility of 11.7 mg/L, it is considered to be difficult to test. Therefore, the following specifications must be met:

Reporting of the methodology and results

a) the test design is reported (nominal concentrations, source of dilution water);

b) the test procedure is reported (e.g. age of Daphnia, composition of the test medium (e.g. particulate matter and total organic carbon), loading in number of Daphnia per test vessel per control);

c) the number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation;

d) the dissolved oxygen measured at least at the beginning and end of the test is reported;

e) adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;

f) as explained above, the Substance is considered to be difficult to test. Therefore the following additional information must be provided:

- the results of a preliminary solubility and stability studies,
- a description of the methods used to prepare stock and test solutions, and
- if the test material is tested at the saturation concentration, evidence that all reasonable efforts have been taken to achieve a saturation concentration.

68 However, in the provided study, you did not report the information listed in a)-f) above.

69 In your comments to the draft decision, you acknowledge the fact that the information specified above is currently not available in the dossier. You provide the following additional information:

a) Five concentrations and control were used in the study, but only highest measured concentration is reported. The reconstituted water according to EPA-66./3-75-009 Method was used as dilution water. ECHA acknowledges that your comments addressed this point;

b) Daphnia magna ≤ 24 h old were used. The composition of the test medium fulfils the conditions specified in the EPA-66./3-75-009 Method, ECHA acknowledges that your comments addressed this point;

c) You state that effect was considered when more than 10 % of immobilisation was detected and no effects were found up to the highest test concentration. Hence you consider that the information in not relevant nor necessary for the assessment of the study. However you still do not provide the raw data to substantiate your claim (i.e., you provide only EC50(48h) value of > 0.02 mg/L);

d) The dissolved oxygen was measured at 0, 24 and 48h in all test vessels but measured values are nor reported. However, you consider this information not critical for rejecting the study. ECHA points out that this is one of the validity criteria of the OECD TG 202;

e) you state that the LOD and LOQ were not reported in the original study report.

f) In your comments to the draft decision, you state that, as the Substance was measured and detected and no effect was observed up to the highest concentration tested, you consider no additional information is needed. However, in the absence of this information, you still fail to demonstrate that exposure to the test material was maximised (i.e. the highest tested concentration was consistent with the saturation concentration of the test material in the test medium).

70 ECHA takes note of the additional information provided in your comments which partially resolve the issues identified above. However, the reporting of the study remains insufficient to conduct an independent assessment of its reliability. More specifically, as you have not provided the information listed under points c), d), e) and f), ECHA is not in a position to assess whether the validity criteria of the test guideline were met, whether the test conducted under conditions that are consistent with the requirement of the OECD TG 202 in combination with the OECD GD 23, and to assess the interpretation of the study results. Furthermore, as the additional information from your comments on the draft decision is not yet in your dossier, the corresponding deficiencies remain. Therefore, the information provided in your comments does not change the assessment outcome. You remain responsible for complying with this decision by the set deadline.

71 On this basis, the specifications of OECD TG 202 are not met.

72 Therefore, this information requirement is not fulfilled.

2.3. Study design and test specifications

73 The Substance is difficult to test due to the low water solubility (11.7 mg/L). 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.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

75 You have provided a growth inhibition study on algae (1995) with the Substance.

3.2. Assessment of the information provided

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

76 To fulfil the information requirement, a study must comply with OECD TG 201 and the specifications of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Based on all information available on the Substance, in particular water solubility of 11.7 mg/L, it is considered to be difficult to test. Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;

Reporting of the methodology and results

b) the test design is reported (*e.g.* nominal concentration(s), number of vessels per control);

c) the test conditions are reported (*e.g.*, composition of the test medium, biomass density at the beginning and at the end of the test);

d) the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported. Algal biomass is normally determined based on dry weight per volume, or alternatively as cell counts or biovolume using microscopy or an electric particle counter. If an alternative method is used (e.g. flow cytometry, *in vitro* or *in vivo* fluorescence, or optical density), a satisfactory correlation with biomass must be demonstrated over the range of biomass occurring in the test;

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

f) adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;

g) as explained above, the Substance is considered to be difficult to test. Therefore the following additional information must be provided:

- the results of a preliminary solubility and stability studies,
- a description of the methods used to prepare stock and test solutions, and
- if the test material is tested at the saturation concentration, evidence that all reasonable efforts have been taken to achieve a saturation concentration.

77 In the provided study:

Technical specifications impacting the sensitivity/reliability of the test

a) the number of replicates was 2 at each test concentration, and you do not specify in your dossier the number of replicates for the control. In your comments to the draft decision, you provide information that the study was performed with duplicates with 10 organisms per test vessel. Further, you provide justification that the test was preformed according to the EPA capricornutum printz algal assay (1978) which allows for the test to be conducted with duplicates. You consider this deviation does not have any impact the sensitivity/reliability of the study (i), as no effects were observed during the test. ECHA notes that the deviation and your justification may be acceptable, however, your comments on the number of test organisms (i.e., 10 organisms) does not seem to be correct for an algae study.

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b) on the test design, you have not specified in your dossier the information listed above. In your comment to the draft decision, you state that five nominal concentrations and a control was used in the test, but only the highest measured concentration is (2.1 mg/L) is reported. You argue that as no effects were detected up to the highest tested concentration, the information on the other concentrations is not needed and hence not relevant for the assessment of the study. ECHA acknowledges that information provided in your comments address the issue;

c) on the test conditions, you have not specified in your dossier the information listed above. In your comments to the draft decision, you acknowledge that biomass density should be reported. However, you argue that as no effects were found up to the highest test concentration, you consider that this information is not relevant and not necessary for the assessment. ECHA reiterates that, without this information, it cannot be assessed whether this study was conducted under conditions that are consistent with the specifications of the OECD TG 201;

d) you report that algal biomass was determined based on *in vivo* chlorophyll-a measurements. However, you have not reported in your dossier evidence of correlation between the measured parameter and dry weight or cell numbers over the range of biomass occurring in the test. In your comments to the draft decision, you acknowledge that the information should be reported. However, as the method is supported by ECHA's standard procedure and as no effects were found up to the highest tested concentrations, you consider this information irrelevant and unnecessary for the assessment of the study (i). ECHA points out that, while *in vivo* chlorophyll-a may be considered a valid method, it is still required to demonstrate that it correlates well to biomass under the conditions of the study;

e) tabulated data on the algal biomass determined daily for each treatment group and control are not reported in your dossier. In your comments to the draft decision, you acknowledge that the information should be reported. However, you consider that the information is not relevant and necessary of the assessment of the study as no effects was observed up to the highest test concentration. ECHA reiterates that without this information, it is no possible to verify that the study met the validity criteria of the OECD TG 201;

f) on the analytical method adequate information, *i.e.* performance parameters of the method are not reported in your dossier. In your comment to the draft decision, you do not provide new information and you state that minimum detectable levels were established, detection limits (LOD/LOQ) are not specified in the study report. Therefore the information is still missing;

g) You did not provide in your dossier the information listed above. In your comments to the draft decision, you state that as the Substance was measured and detected and no effects were observed up to the highest concentration tested, you consider no additional information is needed. However, in the absence of this information, you still fail to demonstrate that exposure to the test material was maximised (i.e. the highest tested concentration was consistent with the saturation concentration of the test material in the test medium).

78 ECHA takes note of the additional information provided which partially resolve the issues identified above. However, the reporting of the study remains insufficient to conduct an independent assessment of its reliability. More specifically, as you have not provided the information listed under points c), d), f) and g) above, ECHA is not in a position to assess whether the validity criteria of the test guideline were met, whether the test conducted under conditions that are consistent with the requirement of the OECD TG 201 in combination with the OECD GD 23, and to assess the interpretation of the study results. Furthermore, as the additional information from your comments on the draft decision is not yet in your dossier, the corresponding deficiencies remain. Therefore, the information provided in your comments does not change the assessment outcome. You remain responsible for complying with this decision by the set deadline.

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

80 Therefore, the information requirement is not fulfilled.

3.3. Study design and test specifications

81 OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under request 2.

4. Ready biodegradability

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

4.1. Information provided

83 You have provided:

(i) a ready biodegradability study (1984), performed according to the OECD TG 301B with the Substance

(ii) a non-guideline biodegradability study using river water as inoculum (Publication, 1976) with the Substance

(iii) a non-guideline biodegradability study using activated sludge as inoculum (Publication, 1976) with the Substance.

84 In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of weight of evidence according to Annex XI, Section 1.2, of the REACH Regulation, based on the studies (i)-(iii) above. In addition, you indicate your intention to include the following additional source of information:

(iv) QSAR predictions with EpiSuite (BIOWIN v4.10).

4.2. Assessment of the information provided in your dossier

4.2.1. The studies (i)-(iii) does not meet the specifications of the test guideline

85 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 specifications must be met:

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.

Technical specifications impacting the sensitivity/reliability of the test

b) the inoculum is not pre-adapted to the test material;

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c) the source of the inoculum, its concentration in the test and any pre-conditioning treatment are reported.

In the studies (i) to (iii):

Key parameter to be measured

a) the ultimate aerobic biodegradation of the test material was not measured as you state in your dossier that "*the test material was evaluated for primary biodegradation in river water sample*" in the study (ii). In your comments to the draft decision, you state that not only study (ii) but also the study (iii) is intended for determination of primary biodegradation.

Technical specifications impacting the sensitivity/reliability of the test

b) the inoculum was pre-adapted to the test material in the studies (i) and (iii);

Reporting of the methodology and results

c) the concentration of the inoculum is not reported in your dossier in any of the reported studies. In your comments to the draft decision, you describe the inoculum in study (i) as: "0.1 g/L of organically rich soil, 0.2 ml/L of fresh aerated mixed liquor obtained from an activated sludge treatment plant and 5 ml/l of raw domestic influent sewage". Based on the information you provided, it can be concluded that the inoculum preparation in study (i) led to a suspended solid concentration above the maximum value allowed by the test guideline (i.e. 30 mg/L). Furthermore, you still fail to provide information on bacterial cell density.

86 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the key parameter of the OECD TG 301/310 is not covered in studies (ii) and (iii). In addition, adapted inoculum was used in the studies (i) and (iii) and thus they cannot be regarded as ready biodegradability study. Finally, based on the information provided in your comments, the inoculum preparation in study (i) led to a suspended solid concentration above the maximum value allowed by the corresponding test guideline (while cellular density remains unknown). On this basis, it can be assumed that the inoculum density was too high and led to conditions that were too favourable.

- the reporting of the studies (ii) and (iii) is not sufficient to conduct an independent assessment of the reliability of the provided study. In particular, it cannot be verified that inoculum density was within the required range specified in the OECD TG 301/310.

87 On this basis, the specifications of OECD TG 301 are not met.

4.3. Assessment of the information provided in your comments to the draft decision

4.3.1. Weight of evidence adaptation rejected

88 In addition to the deficiencies identified in Section 0.2., ECHA identified endpoint specific issue(s) addressed below.

4.3.1.1. the sources of information (i)-(iii) are not relevant

89 As explained under Section 0.2 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 the information requirement of Annex VII, Section 9.2.1.1. includes similar information that is produced by the OECD TG 301/310. OECD TG 203 requires the study to investigate the following key element:

- 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.

91 As explained in Section 4.2.1. above, the sources of information (i)-(iii) does not provide information on ultimate aerobic biodegradation. This is because sources of information (ii) and (iii) inform on primary degradation and not on ultimate degradation and source of information (i) was not conducted under low inoculum concentration.

92 Therefore, the source of information (i)-(iii) are considered relevant for ready biodegradation.

93 The sources of information (iv) may provide relevant information on ultimate aerobic biodegradation. However, the reliability of the source of information (iv) is affected by the following deficiencies.

4.3.1.2. Currently no information on the QSAR prediction available

94 In your comments to draft decision, you indicate your intention to provide QSAR prediction as additional source of information to support your conclusion that the Substance is readily biodegradable. However, you fail to provide sufficient information for the prediction in the form of a QSAR Prediction Reporting Format (QPRF). Therefore, the information in your comments is not sufficient for ECHA to make an independent assessment.

4.3.1.3. Conclusion on your weight-of-evidence adaptation

95 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information based on which a conclusion on the information requirement can be drawn.

96 Furthermore, ECHA points out that Guidance on IRs and CSA, Section R.7.9.5.1. specifies that QSAR prediction alone is not sufficient to fulfil the information requirement under Annex VII, Section 9.2.1.1. However, when no useful information on degradability is available (either experimentally derived or estimated), (Q)SAR predictions can be used as supporting evidence of that the substance is not rapidly degradable.

97 For the reasons already explained under Section 4.3.1.1., your dossier or your comments on the draft decision do not include any other relevant source of information to support your conclusion that the Substance should be regarded as readily biodegradable. Therefore, this information alone cannot be regarded as sufficient justification for your weight of evidence adaptation.

98 In summary, the sources of information (i)-(iii) do not provide information on ultimate aerobic biodegradation. Furthermore, you do not provide any documentation on source of information (iv) and therefore ECHA cannot assess its reliability. Finally, as explained above, in the absence of other sources of information supporting your conclusion, source of information (iv) is not sufficient on its own to conclude the Substance is readily biodegradable.

99 Accordingly, 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 an OECD TG 301/310 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Reasons related to the information under Annex VIII of REACH

5. *In vitro* micronucleus study

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

5.1. Information provided

101 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) an *in vitro* mammalian chromosomal aberration test (2000) with the source substance diisononyl phthalate, EC 271-090-9

(ii) an *in vivo* mammalian erythrocyte micronucleus test (2000) with the source substance diisononyl phthalate, EC 271-090-9

(iii) an *in vivo* mammalian erythrocyte micronucleus test (2000) with the source substance diisodecyl phthalate, EC 271-091-4

5.2. Assessment of the information provided

5.2.1. Read-across adaptation rejected

102 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.

103 Therefore, the information requirement is not fulfilled.

5.3. Specification of the study design

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

5.3.1. Assessment of aneugenicity potential

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

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

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

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

107 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 or a general adaptation rule under Annex XI.

6.1. Information provided

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

(i) A short-term repeated dose toxicity study with the Substance (1987)

(ii) A short-term repeated dose toxicity study with the Substance (2009)

109 In the comments to the draft decision, you state that the following studies, which are already included in your dossier, inform on gross pathology and histopathology:

(iii) Combined Chronic Toxicity / Carcinogenicity Study (1997) with the source substance EC 271-090-9

(iv) repeated Dose 90-Day Oral Toxicity Study in Non-Rodents (1999) with the source substance EC 271-090-9

(v) sub-chronic toxicity study in rats and dogs (1973) with the source substance EC 271-091-4.

110 ECHA understands that you intend to expand your weight of evidence adaptation to include studies (iii) – (v). However, as explained under section '8.2.1.4 Reliability of the contribution of the information on the analogue substances', these studies are affected by such significant deficiencies that they cannot reliably contribute to your Annex XI, Section 1.2. (weight of evidence) adaptation.

111 As explained in Section 0.2., your adaptation based on weight of evidence under Annex XI, Section 1.2. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

6.2. Assessment of information provided

6.2.1. Weight of evidence adaptation rejected

112 As explained under Section 0.2 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.

113 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.1 at Annex VIII includes, at general level, 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.

Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system. This information is covered by information similar to OECD TG 407.

6.2.1.1. In-life observations

114 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).

115 The source of information (i) may provide relevant information on body weight. Study (ii) may provide relevant information on survival, body weight development, clinical signs, functional observations, and food/water consumption. None of the studies provided information on functional observations.

6.2.2. Blood chemistry

116 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).

117 The sources of information (i) and (ii) may provide relevant information on blood chemistry.

6.2.3. Organ and tissue toxicity

118 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).

119 The source of information (i) may provide relevant information on liver weight. The source of information (ii) may provide relevant information on organ weights.

120 In the comments to the draft decision, you state that studies (iii) – (v) inform on gross pathology and histopathology. Studies (iii) and (iv) may indeed inform on gross pathology and histopathology. However, the robust study summaries provided for study (v) do not report any details on whether organ and tissue toxicity were studied.

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

6.2.4. The provided sources of information are not reliable due to technical deficiencies

122 To fulfil the information requirement, normally a study according to OECD TG 407 (2008) must be provided. The OECD TG 407 specifies that:

a) testing is performed with at least three dose levels (unless conducted at the limit dose) and with concurrent controls;

b) at least 5 male and 5 female animals are used for each concentration and control group;

c) dosing of the test substance is performed daily for a minimum of 28 days.

123 The reported data for the studies you have provided did not include:

a) only one dose level was described (ii);

b) No females were included in each test and control group (ii);

c) the exposure duration was limited to 21 days (i).

124 In summary, all the sources of information (i) to (ii) have a critical issue with regard to missing investigations from the study normally expected to meet this information requirement (i.e., functional observations, gross pathology and histopathology). In addition, the sources of information (i) to (ii) have other significant reliability issues and cannot therefore contribute to the conclusion on short-term repeated-dose toxicity of the Substance.

125 In the comments to the draft decision, you acknowledge the reliability issues listed above. However, you do not provide any new information that addresses the reliability issues identified above. Although studies (iii) and (iv) may inform on gross pathology and histopathology, they are vitiated by significant deficiencies for the reasons listed under section '8.2.1.4 Reliability of the contribution of the information on the analogue substances'. In addition, the robust study summary provided for study (v) does not report any details on whether organ and tissue toxicity were studied.

6.3. Conclusion

126 As a conclusion, the sources of information as indicated above, provide information on short-term repeated-dose toxicity. However, the reliability of this information is severely impacted by the issues listed above.

127 Accordingly, 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 an OECD TG 407 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

6.4. Specification of the study design

128 Following the criteria provided in Annex VIII, Section 8.6.1., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.1., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance.

129 According to the OECD TG 407, the rat is the preferred species.

130 Therefore, the study must be performed according to the OECD TG 407, in rats and with oral administration of the Substance.

6.4.1. Justification for an adaptation of the short-term repeated dose toxicity study (Annex VIII, Section 8.6.1., Column 2)

131 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 8).

132 According to Annex VIII, Section 8.6.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not need to be conducted. Therefore, to comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to provide a justification for adaptation, as provided in Annex VIII, Section 8.6.1., Column 2.

133 In case the adopted decision no longer contains a request for a 90-day study, you are required to provide a 28-day study.

134 Therefore, you are requested to either submit:

- a justification for the adaptation according to Annex VIII, Section 8.6.1., Column 2, based on request 8; or
- a 28-day study as per the study design described in 6.4 in case the 90-day study is not requested in the adopted decision.

7. Short-term toxicity testing on fish

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

7.1. Information provided

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

(i) A short-term toxicity study on *Pimephales promelas* under static conditions (publication, 1995) with the Substance;

(ii) A short-term toxicity study on *Pimephales promelas* under flow-through conditions (publication, 1995) with the Substance;

(iii) A short-term toxicity study on *Oncorhynchus mykiss* under flow-through conditions (publication, 1995) with the Substance;

7.2. Assessment of the information provided

7.2.1. Weight of evidence adaptation rejected

137 As explained under Section 0.2 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.

138 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 9.1.3. includes similar information that is produced by the OECD TG 203. OECD TG 203 requires the study to investigate the following key element:

- the concentration of the test material leading to the mortality of 50% of the juvenile fish at the end of the test is estimated;

139 The sources of information (i), (ii) and (iii) provide relevant information on this key element.

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

7.2.1.1. The reliability of the sources of information cannot be assessed

140 To fulfil the information requirement, normally a study according to OECD TG 203 must be provided. In addition, if the test material is difficult to test, the requirements of the OECD GD 23 must be followed (Article 13(3) of REACH). Based on all information available on the Substance, in particular water solubility of 11.7 mg/L, it is considered to be difficult to test. The OECD TG 203 in combination with the OECD GD 23 specifies that:

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a) the test procedure is reported (composition of the test medium, fish loading, nominal concentration(s));

b) adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations are provided;

c) as explained above, the Substance is considered to be difficult to test. Therefore the following additional information must be provided:

- the results of a preliminary solubility and stability studies,
- a description of the methods used to prepare stock and test solutions, and
- if the test material is tested at the saturation concentration, evidence that all reasonable efforts have been taken to achieve a saturation concentration.

In the provided sources of information (i) and (ii):

Reporting of the methodology and results

a) on the test procedure, you have not specified the parameters listed above for any of the sources of information.

b) on the analytical method, adequate information, i.e. performance parameters of the method are not reported for any of the sources of information. In addition, the results of the analytically determined exposure concentrations are not provided for all the test concentrations (i.e. only highest measured concentrations were reported).

c) You did not provide the information for any of the sources of information.

141 In your comments to the draft decision, you acknowledge the fact that the information specified above is currently not available in the dossier. You provide the following additional information:

a) You state that the test medium was in accordance with EPA-660/3-75-009. Fish loading was according to EPA-660/3-75-009 with maximum fish loading of 0.8 g/L and 2g/L for static and flow-through, test respectively. Five concentrations and control were used in the study, but only the highest measured concentration is reported. As no effect was observed, you consider the information on other test concentrations not relevant for the assessment of the study. ECHA acknowledge that your comments address this point;

b) You did not provide new information on the analytical method and you state that minimum detectable levels were established but detection limits (LOD/LOQ) are not specified in the study report. You state that only the highest measured concentration is reported. Therefore the information is still missing;

c) In your comments to the draft decision, You state that as the Substance was measured and detected and no effect was observed up to the highest concentration tested, you consider no additional information is needed. However, in the absence of this information, you still fail to demonstrate that exposure to the test material was maximised (i.e. the highest tested concentration was consistent with the saturation concentration of the test material in the test medium).

142 ECHA takes note of the additional information provided which partially resolve the issues identified above. However, you still fail provide adequate information addressed for the

points b) and c) above. In the absence of the above information, it is not possible to conduct an independent assessment as to ascertain the extent to which the sources of information (i) and (ii) were or were not conducted under conditions that are set out in the OECD TG 203 in combination with the OECD GD 23, and whether the interpretation of the results is adequate. Furthermore, as the additional information from your comments on the draft decision is not yet in your dossier, the corresponding deficiencies remain.

143 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

7.2.1.2. Conclusion

144 As a conclusion, the sources of information as indicated above, provide information on short-term toxicity on fish. However, the reliability of this information is severely impacted by the issues listed above.

145 Accordingly, 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 an OECD TG 203 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

7.3. Study design and test specifications

146 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.

Reasons related to the information under Annex IX of REACH

8. Sub-chronic toxicity study (90 days)

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

8.1. Information provided

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

(i) a Combined Chronic Toxicity / Carcinogenicity Study (1997) with the source substance diisononyl phthalate, EC 271-090-9

(ii) a Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents (1999) with the source substance diisononyl phthalate, EC 271-090-9

(iii) a sub-chronic toxicity in rats (1973) with the source substance diisodecyl phthalate, EC 271-091-4

(iv) a sub-chronic toxicity in dogs (1973) with the source substance diisodecyl phthalate, EC 271-091-4

149 As explained in Section 0.2., your adaptation based on weight of evidence under Annex XI, Section 1.2. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

8.2. Assessment of information provided

150 As explained under Section 0.2 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.

151 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes, at general level, 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. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system. This information is covered by information similar to OECD TG 408.

8.2.1.1. In-life observations

152 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).

153 Studies (i) and (ii) may provide relevant information on in-life observations, with the exception of functional observations. You do not report any details on whether in-life observations were studied in (iii) and (iv).

8.2.1.2. Blood chemistry

154 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)

155 Studies (i) and (ii) may provide relevant information on blood chemistry. You do not report any details on whether blood chemistry was studied in (iii) and (iv).

8.2.1.3. Organ and tissue toxicity

156 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).

157 Studies (i) and (ii) may provide relevant information on organ and tissue toxicity. You do not report any details on whether organ and tissue toxicity was studied in (iii) and (iv).

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

8.2.1.4. Reliability of the contribution of the information on the analogue substances

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

8.2.1.4.1. The provided sources of information (ii) to (iv) are not reliable due to technical deficiencies

160 To fulfil the information requirement, normally a study according to OECD TG 408 must be provided. The OECD TG 408 specifies that:

a) testing is performed with at least three dose levels (unless conducted at the limit dose) and with concurrent controls;

b) the highest dose level should aim to induce toxicity or reach the limit dose;

c) at least 10 male and 10 female animals are used for each concentration and control group.

161 The studies (ii) to (iv) are described as chronic or sub-chronic repeated dose toxicity studies. However, the following specifications are not according to the requirements of OECD TG 408:

a) the number of dose levels and concurrent controls were not described (iii, iv);

b) you do not provide any justification for the dose setting and provide no details on the highest dose used (iii, iv);

c) only 4 males and 4 females were included in each test and control group (ii). For studies (iii) and (iv) no details on the number of animals used is provided;

162 In summary, all the sources of information (ii) to (iv) have a critical issue with regard to missing investigations from the study normally expected to meet this information requirement. In addition, the sources of information (iii) and (iv) have a critical reliability issue with regard to not having any data on the number of animals used and doses used. This information is required respectively to assess the statistical power of the study and to determine whether the doses were high enough to cause toxicity. Without such information ECHA cannot evaluate the reliability of the conclusions. Finally, the number of animals used in study (ii) is so low that the study does not have the required statistical power and is in turn unreliable.

163 In the comments to the draft decision, you acknowledge the reliability issues listed above. However, You do not provide any new information that addresses these issues.

8.3. Conclusion

164 As a conclusion, the sources of information as indicated above, provide information on short-term repeated-dose toxicity (90 days). However, the reliability of this information is severely impacted by the issues listed above.

165 Accordingly, 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 an OECD TG 408 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

8.4. Specification of the study design

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

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

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

9. Long-term toxicity testing on aquatic invertebrates

169 Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

9.1. Information provided

170 You have provided a non-guideline long-term toxicity study on *Daphnia magna* (1995) with the Substance.

9.2. Assessment of the information provided

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

171 To fulfil the information requirement, a study must comply with the OECD TG 211 and the specifications of OECD GD 23 if the substance is difficult to test (Article 13(3) of

REACH). Based on all information available on the Substance, in particular water solubility of 11.7 mg/L, it is considered to be difficult to test. Therefore, the following specifications must be met:

Reporting of the methodology and results

a) the test procedure is reported (e.g. loading in number of *Daphnia* per litre, composition of the test medium including the DOC/TOC content);

b) the nominal test concentrations and the results of all analyses to determine the concentration of the test substance in the test vessels are reported;

c) adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;

d) as explained above, the Substance is considered to be difficult to test. Therefore the following additional information must be provided:

- the results of a preliminary solubility and stability studies,
- a description of the methods used to prepare stock and test solutions, and
- if the test material is tested at the saturation concentration, evidence that all reasonable efforts have been taken to achieve a saturation concentration.

172 In study (i):

Reporting of the methodology and results

a) -d) You did not report any of the information listed above.

173 In your comments to the draft decision, you acknowledge the fact that the information specified above is currently not available in the dossier and you provide the following additional information on study (i):

a) On the test procedure, you report that 20 daphnids were held in 50 ml test solution. You describe the source of test medium as "fortified well water." You state that there is no information on DOC/TOC. However, you consider that the lack of information on TOC does not critically affect the reliability of the study (i). However, ECHA considers that as natural water was used as test medium and you do not provide any information on purification procedure, it is not possible to evaluate potential TOC content of the test medium;

b) You state that only mean measured concentrations are available and you provide standard deviations of the measured concentrations;

c) You did not provide additional information on the analytical method;

d) You state that as the Substance was measured and detected and no effect was observed at all concentrations, you consider no additional information is needed. However, in the absence of this information, you still fail to demonstrate that exposure to the test material was maximised (i.e. the highest tested concentration was consistent with the saturation concentration of the test material in the test medium).However, provided information still does not demonstrate that the exposure concentration of the test material was maximised in the test solution .

174 ECHA takes note of the additional information provided which partially resolve the issues identified above. However, you still fail provide adequate information addressed for the points a), c) and d) above. Therefore, it cannot be assessed whether the study was conducted under conditions that are consistent with the requirements of the OECD TG 211 in combination with the OECD GD 23, and to assess the interpretation of the results

is adequate. Furthermore, as the additional information from your comments on the draft decision is not yet in your dossier, the corresponding deficiencies remain. Therefore, the information provided in your comments does not change the assessment outcome. You remain responsible for complying with this decision by the set deadline.

175 On this basis, the specifications of OECD TG 211 are not met.

176 Therefore, the information requirement is not fulfilled.

9.3. Study design and test specifications

177 OECD TG 211 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under request 2.

References

The following documents may have been cited in the decision.

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

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

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).
All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

The information requirement for an Extended One-Generation Reproductive Toxicity Study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. The EOGRTS may be addressed in a separate decision once the information from the sub-chronic toxicity study (90 days) requested in this decision is provided; because the results from the 90-day study are needed for the design of the EOGRTS. Similarly the information requirement for a screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

The information requirement for long-term toxicity testing on fish (Annex IX, Section 9.1.6.) is not addressed in this decision. This is because information that will be generated from the studies requested in the present decision is needed:

- to inform on the potential endocrine disrupting properties of the Substance; and
- to decide on the most appropriate test(s) to meet the information requirement.

The above information requirements may be addressed in a separate decision at a later stage.

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 07 December 2021.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. The standard deadline granted by ECHA has been exceptionally extended by 6 months for request 4 and by 24 months for all other information requests to take into account currently longer lead times in contract research organisations and the fact that ECHA has also notified draft decisions to other members of the group of High Molecular Weight Phthalates (HMWP).

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

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

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

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

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

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

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- 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[3].

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

1.2. Test material

(1) Selection of the Test material(s)

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

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

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

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values.

With that detailed information, ECHA can confirm 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 (https://echa.europa.eu/manuals).

References to Guidance on REACH and other supporting documents can be found in Appendix 1.

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