~~Confidential~~

Helsinki, 11 October 2023

Addressees
Registrants of JS_3648-20-2 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
26/03/2015

Registered substance subject to this decision ("the Substance")
Substance name: Diundecyl phthalate, branched and linear
EC number/List number: 287-401-6

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 5 below by ***16 January 2025*** and all other information listed below by ***16 November 2027***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.)
   a) *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and
   b) only if the *in vitro/in chemico* test methods specified under point a) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429);

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

3. Long-term toxicity testing on aquatic invertebrates, also requested below (triggered by Annex VII, Section 9.1.1., Column 2)

4. Growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3/OECD TG 201)

5. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: EU C.4. C/D/E/F/OECD TG 301B/C/D/F or EU C.29./OECD TG 310) on relevant constituent(s)/fraction(s) of the Substance, as described under the corresponding appendix on reasons for the request

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

6. *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

7. 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 study (28 days) (Annex VIII, Section 8.6.1.; test method: EU B.7/OECD TG 407) by oral route, in rats

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. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat)

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

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

11. Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit)

The reasons for the requests are explained in Appendix 1.

Information required depends on your tonnage band

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

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

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

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

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

Appendix 1: Reasons for the request(s)

Contents

Reasons common to several requests 5

Reasons related to the information under Annex VII of REACH 11

1. Skin sensitisation 11
2. *In vitro* gene mutation study in bacteria 12
3. Long-term toxicity testing on aquatic invertebrates 13
4. Growth inhibition study aquatic plants 13
5. Ready biodegradability 16

Reasons related to the information under Annex VIII of REACH 19

6. *In vitro* micronucleus study 19
7. Short-term repeated dose toxicity (28 days) 20

Reasons related to the information under Annex IX of REACH 23

8. Sub-chronic toxicity study (90 days) 23
9. Pre-natal developmental toxicity study in one species 24
10. Long-term toxicity testing on aquatic invertebrates 26

Reasons related to the information under Annex X of REACH 30

11. Pre-natal developmental toxicity study in a second species 30

References 31

Reasons common to several requests

0.1. Test material not representative of the Substance

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

2 The studies submitted for ready biodegradability and in vitro micronucleus have been conducted with the Substance without further information on the distribution of alkyl chain length and information on the branching of alkyl side carbon chain (i.e., isomeric composition).

3 In the absence of detailed information on the UVCB test material, such as the distribution of alkyl chain length and information on the branching of alkyl side carbon chain (i.e., isomeric composition), the identity of the test material cannot be assessed. Therefore you have not demonstrated that the test material is representative for the Substance.

0.2. Read-across adaptation rejected

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

- Skin sensitisation (Annex VII, Section 8.3.)
- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

5 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.

6 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.

7 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. Scope of the grouping of substances (category)

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

9 For the purpose of this decision, ECHA understands that the following category members are listed in the read-across justification document:

- The Substance
- Diundecyl phthalate, EC 222-884-9 (source substance 1)
- Didodecyl phthalate, EC 219-415-5 (source substance 2)
- Dinonyl phthalate, EC 201-560-0 (source substance 3)
- Didecyl phthalate, EC 201-561-6 (source substance 4)
- Nonyl undecyl phthalate, EC 265-603-5 (source substance 5)
- 1,2-Benzenedicarboxylic acid, di-C9-11-alkyl esters, EC 272-012-6 (source substance 6)
- 1,2-benzenedicarboxylic acid, di-C8-10-alkyl ester, EC 275-809-7 (source substance 7)
- Decyl nonyl phthalate, EC 306-154-8 (source substance 8)
- Isodecyl octyl phthalate, EC 215-554-0 (source substance 9)
- Decyl isooctyl phthalate, EC 258-498-2 (source substance 10)
- 1,2-benzenedicarboxylic acid, mixed isodecyl and tridecyl diesters, CAS No. 68648-95-3 (source substance 11)
- Isoundecyl nonyl phthalate, EC 306-156-9 (source substance 12)
- Isoundecyl undecyl phthalate, EC 306-157-4 (source substance 13)
- Isononyl undecyl phthalate, EC 306-161-6 (source substance 14)
- 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, EC 271-085-1 (source substance 15)

10 In your read across justification document (section 4.0) you state that "*Reliable data are also available for* [...] *1,2- benzenedicarboxylic acid, di-C6-10-alkyl esters – L6-10P (CAS No. 68515-51-5)*". Although you do not list it in the table of source substances (section 4.0 of your read across justification document), ECHA understands that you also consider the following source substance as a category member:

- 1,2- benzenedicarboxylic acid, di-C6-10-alkyl esters – L6-10P, EC 271-094-0, CAS No. 68515-51-5 (source substance 16)

11 You justify the grouping of the substances as substances with:

- a common functional group;
- common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or
- a constant pattern in the changing of the potency of the properties across the group.

12 You explain that the US EPA HPV challenge program defined the "phthalate esters" category based on the parameters listed above, and specified the following criterium: "*1,2-benzenedicarboxylic acids, with side chain esters ranging in carbon chain length from C1 to C13*".

13 You then define the following three sub-categories by referring to US EPA HPV program:

- Low molecular weight phthalates produced from alcohols with straight-chain carbon backbones of <C3.
- Transitional phthalates produced from alcohols with straight-chain carbon backbones of C4-6
- High molecular weight phthalates produced from alcohols with straight-chain carbon backbones of >C7 or a ring structure.

14 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 includes substances with side chains ranging from C7 to 13. The side chain may be a linear, branched, a benzyl group or a combination of those.

15 We have identified the following issues with the determination of the scope of the grouping fo substances:

0.2.1.1. Incomplete characterisation of the category members

16 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 group*".

17 Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substances must be provided, to the extent that this is measurable, to allow assessing whether the attempted predictions are compromised by the composition and/or impurities (Guidance on IRs and CSA, Section R.6.2.5.5.).

18 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.

19 For the source substances 1 to 4 you have not provided information on isomeric composition and its branching of alkyl side carbon chain.

20 In addition, the studies addressed in requests 1, 2, 4, 5, 7, 8, 9 and 10 have been conducted with the source substances 1, 7, 15, and/or 16, contain only limited information besides CAS and EC numbers.

21 More specifically, you have only provided:

- In a repeated dose toxicity study with EC 275-809-7 (1993) you claim a purity of [redacted]%.
- In a prenatal developmental toxicity study with EC 271-094-0 (1993) you claim a purity of [redacted]%.
- In two reproductive toxicity studies you claim a purity of [redacted]%/[redacted]% for EC 271-094-0 (1998) and [redacted]% for EC 271-085-1 (1997).

22 In addition, regarding source substance 16 (EC 271-094-0), the name of the substance you provide ("1,2- benzenedicarboxylic acid, di-C6-10-alkyl esters – L6-10P") implies that the source substance may not fall within the boundaries of the "high molecular weight phthalates" category, in terms of chain length.

23 No other information has been provided on purity, composition, carbon chain length, branching, and isomerisation.

24 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.

0.2.2. Predictions for (eco) toxicological properties

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

26 You predict the properties of the Substance from information obtained from the following source substances:

- Diundecyl phthalate, EC 222-884-9 (source substance 1);
- 1,2-benzenedicarboxylic acid, 1,2-benwenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7 (source substance 7);
- 1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0 (source substance 16);
- 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, EC 271-085-1 (source substance 15)

27 You provide the following reasoning for the prediction of (eco) toxicological properties:

- "*Several short-term (acute) and sub-acute mammalian toxicology studies have been carried out on the* target substance using laboratory animals (in vivo studies) or laboratory cell lines (in vitro studies). Similar studies, and those of longer duration, are available on the source substances. The acute toxicity of the group members was comparably low for the oral and dermal routes, being consistently above the limit dose of 2000 mg/kg"
- "The absence of a mutagenic potential was demonstrated for all substances of the group in various guideline in-vitro tests"
- "Due to structural similarities, comparable physical/chemical properties the toxicokinetic profile of the registered substance and the potential structural analogue substances are also expected to be comparable in terms of physiological absorption, distribution, metabolism and excretion processes"
- All substances of the group "*are expected to undergo rapid aerobic biodegradation, have low bioaccumulation potentials and show high adsorption properties" and that they "have a low potential to cause toxicity to water based species including fish, daphnia, algae and microorganisms at the limits of their water solubility which, for all of the substances, is low*".

28 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 substance.

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

0.2.2.1. Insufficient data density

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*".

31 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.

32 You have provided robust study summaries for the following studies:

- One HRIPT with the source substance EC 222-884-9
- One in vitro gene mutation study in bacteria with the source substance EC 222-884-9;

- One in vitro cytogenicity study in mammalian cells with the Substance
- Two repeated dose toxicity studies with source substance EC 222-884-9 and one study with source substance EC 275-809-7.
- Three pre-natal developmental toxicity studies (source substances EC 271-094-0, EC 271-085-1, EC 222-884-9);

33 The proposed category of "high molecular weight phthalates" includes substances with side chains ranging from C7 to 13. The side chain may a linear, branched, a benzyl group or a combination of those. You have not provided any justification as to why the information on one or few category members is sufficient to establish a trend across such broad category considering the variation in C-chain length and the complex isomeric composition that likely originate from the branching of the side-chains. Therefore, the information provided is not sufficient to conclude that (eco)toxicological properties are likely to follow a regular pattern.

0.2.2.2. Missing supporting information to compare properties of the substances

34 Annex XI, Section 1.5. requires that whenever read-across is used "*supporting information to scientifically justify such explanation for prediction of properties*" must be provided. 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.).

35 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).

36 You argue that the Substance and "*the potential structural analogue substances*" have comparable toxicokinetcs and specify that they are "*expected to be comparable in terms of physiological absorption, distribution, metabolism and excretion processes*". However, you have not provided any evidence to support this claim. In turn, you have not demonstrated that toxicokinetic differences or similarities of the group members may affect the prediction of toxicity.

37 In your read-across justification document you have provided a data matrix ('Table 2: Data available regarding human health effects') summarizing the study results on source substances 1, 7, 15, 16, and the Substance. In this table, under "genetic toxicity: in vitro" you state that there are negative results for substances 1, 7, 15, 16, and the Substance. However, you have only provided a robust study summary for an in vitro gene mutation study in bacteria (source substance EC 222-884-9) and an in vitro cytogenicity study in mammalian cells with the Substance. You have not specified the nature of the other in vitro studies and your read-across justification or the registration dossier do not include any robust study summaries for these studies. In 'Table 2' you also list the LD_{50} values obtained with acute toxicity studies with source substances 1, 7, 15, 16, and the Substance. However, the LD_{50} itself is not sufficient to establish that the Substance and the source substances are likely to have similar properties under the standard information requirements listed under 0.2. You provide no further studies (including descriptions in the form of robust study summaries) that bridge the toxicological profile of the Substance with the source substances.

38 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.

0.2.2.3. Inadequate or unreliable source studies

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

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

40 Specific reasons why the studies on the source substance(s) do not meet these criteria are explained further below under the applicable information requirement sections 2, 6, 7, 8 and 10. Therefore, no reliable predictions can be made for these information requirements.

0.2.3. Conclusion on the read-across approach

41 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.

42 In your comments on the draft decision, you acknowledge that "*the documentation to support the adaptation doesn't fulfil the current guidance on the subject - the Read-across assessment framework (RAAF) of March 2017 and RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB) of March 2017*." You describe a strategy to revise your category approach and state that "[s]*hould the read-across approach turn out not to be an adequate option to adapt the information requirements the Registrants will perform the studies as requested*".

43 As this strategy relies essentially on data, which is yet to be generated, no assessment can currently be made by ECHA. You remain responsible for complying with this decision by the set deadline.

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

44 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

1.1. Information provided

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

(i) HRIPT (1999) with the source substance diundecyl phthalate, EC 222-884-9, CAS No. 3648-20-2.

1.2. Assessment of the information provided

1.2.1. Assessment whether the Substance causes skin sensitisation

1.2.1.1. Read-across adaptation rejected

46 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.

47 On this basis, the information provided does not contribute to the assessment whether the Substance causes skin sensitisation.

1.2.2. No assessment of potency

48 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

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

50 Therefore, the information requirement is not fulfilled.

51 In your comments on the draft decision, you state your intent to re-evaluate and, if possible, improve the read-across approach and that if a read-across adaptation is "*not promising*", you will perform the requested studies. As already addressed under '0.2.3 Conclusion on the read-across approach', you propose a strategy to improve your adaptation under Annex XI, Section 1.5. (grouping of substances and read-across approach). However, as this strategy relies essentially on data, which is yet to be generated, no assessment can currently be made by ECHA. You remain responsible for complying with this decision by the set deadline.

1.3. Specification of the study design

52 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of

dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

53 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

2. *In vitro* gene mutation study in bacteria

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

2.1. Information provided

55 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* gene mutation study in bacteria (1985) with the source substance iundecyl phthalate, EC 222-884-9, CAS No. 3648-20-2.

2.2. Assessment of the information provided

2.2.1. Read-across adaptation rejected

56 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. In addition, ECHA identified endpoint specific issue(s) addressed below.

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

57 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 407. 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).

58 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).

59 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, does not provide an adequate coverage of the key parameter of the corresponding OECD TG.

60 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance. Therefore, your read-across approach under Annex XI, Section 1.5. is rejected.

61 Therefore, the information requirement is not fulfilled.

62 ECHA understands from your comments on the draft decision that you agree to conduct the requested study.

2.3. Specification of the study design

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

3. Long-term toxicity testing on aquatic invertebrates

64 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII, Column 1, Section 9.1.1. However, under Column 2, long-term toxicity testing on aquatic invertebrates may be required by the Agency if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

3.1. Triggering of the information requirement

65 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required.

66 In the provided a QSAR prediction (2013) of the saturation concentration of the Substance in water was determined to be 0.033 µg/L.

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

3.2. Information requirement not fulfilled

68 The information provided, its assessment and the specifications of the study design are addressed under request 10.

4. Growth inhibition study aquatic plants

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

4.1. Information provided

70 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) a growth inhibition study on algae performed according to OECD TG 201 (1984) with the source substance Diundecyl phthalate, EC 222-884-9.

4.2. Assessment of the information provided

4.2.1. Read-across adaptation rejected

71 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. In addition, ECHA identified endpoint specific issue(s) addressed below.

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

72 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 201, and meet the specifications of OECD GD 23 if the substance is difficult to test. The source substance is difficult to test due to its low water solubility. Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) at least 6 treatment replicates are included if a limit test (at 100 mg/L or at the limit of solubility of the test substance) is conducted;

Reporting of the methodology and results

b) the test conditions are reported (e.g., biomass density at the beginning of the test);

c) 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;

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

e) as explained above, the tested analogue substance is 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.

73 In study (i):

Technical specifications impacting the sensitivity/reliability of the test

a) the number of replicates was 3 for the test concentration;

Reporting of the methodology and results

b) on the test conditions, you have not specified the biomass density at the beginning of the test;

c) the method used to determine algal biomass is not reported

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

e) The tested analogue substance is difficult to test, and you have not provided the information listed above.

74 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, you have conducted the study with 3 instead of 6 replicates which might had an impact on the variability of the results and the accuracy of the estimated effect values.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, as you have not provided the information listed under point b) to e), 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 requirements of the OECD TG 201 and OECD GD 23, and to assess the interpretation of the study results.

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

76 Therefore, the information requirement is not fulfilled.

77 In your comments to the draft decision, you point out that the study (i) was conducted in 1984, according to the test guideline available at that time. You acknowledge that the study (i) is not fully consistent with the current OECD TG 201. However, you believe that the conclusion of the study (i), namely EC_{10}>3.3 mg/L, is nevertheless reliable. Furthermore, you argue that the reliability of the conclusion is enhanced by the longer duration of the study (8 days), as compared to 72 hr of the OECD TG 201. Finally, you state that the results of the study (i) are further supported by another guideline study on di-C11 ester, resulting in a NOEC of 2.1 mg/L. Finally, you state that the requested study will not lead to additional knowledge nor different conclusion (no effect concentration at the water solubility). Therefore, you disagree with the request and instead of performing the requested study, you indicated your intension to rework on the technical dossier entry in a future update of your registration dossier.

78 However, you do not provide specific information addressing the issues identified above. 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.

4.3. Study design and test specifications

79 The Substance is difficult to test due to the low water solubility (0.033 µg/L) and adsorptive properties (Log K_{oc} of 21.4). OECD TG 201 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 201. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

80 For multi-constituents/UVCBs, the analytical method must be adequate to monitor qualitative and quantitative changes in exposure to the dissolved fraction of the test material during the test (e.g. by comparing mass spectral full-scan GC or HPLC chromatogram peak areas or by using targeted measures of key constituents or groups of constituents).

81 If you decide to use the Water Accommodated Fraction (WAF) approach, in addition to the above, you must:

- use loading rates that are sufficiently low to be in the solubility range of most constituents (or that are consistent with the PEC value). This condition is mandatory to provide relevant information for the hazard and risk assessment (Guidance on Irs and CSA, Appendix R.7.8.1-1, Table R.7.8-3);
- provide a full description of the method used to prepare the WAF (including, among others, loading rates, details on the mixing procedure, method to separate any remaining non-dissolved test material including a justification for the separation technique);
- prepare WAFs separately for each dose level (*i.e.* loading rate) and in a consistent manner.

5. Ready biodegradability

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

5.1. Information provided

83 You have provided:

(i) a ready biodegradability study performed according to the EU Method C.4.C (2010) with the Substance;

(ii) a prediction from QSAR BIOWIN v4.10 (2013);

(iii) a ready biodegradability study performed according to the EPA560/6-82-003 (1984) with the source substance Diundecyl phthalate, EC 222-884-9.

5.2. Assessment of the information provided

5.2.1. Test material in study (i) not representative of the Substance

84 As explained in Section 0.1., the test material in study (i) is not representative of the Substance. In addition, ECHA identified the endpoint-specific issues addressed below.

5.2.2. Ready biodegradation tests are normally intended for pure substances

85 The revised introduction to the OECD Guidelines For Testing Of Chemicals, Section 3 Part I states that ready biodegradability tests are intended for pure substances but may also be relevant, on a case-by-case basis, to mixtures of structurally similar chemicals (i.e. which are composed of constituents expected to show similar degradation kinetics). However, such tests are not generally applicable for complex mixtures or substances (i.e. UVCB or multi-constituent substances) containing different types of constituents. For complex substances, a single ready biodegradability test does not allow to conclude on the ready

biodegradability of all constituents and therefore, does not fulfil the information requirement.

86 You have provided the studies (i) and (iii) conducted on multi-constituent or UVCB substances. These substances are complex substances and contain constituents with significant structural differences as they differ in terms of the distribution of alkyl chain length and the branching of alkyl side carbon chain (i.e., isomeric composition).

87 In your comment to the draft decision, you argue that the Substance consists of structurally similar chemicals and hence you consider that the ready biodegradability study is applicable to the Substance. Furthermore, you argue that the shape of the degradation curve allows to draw conclusion on the degradability of the entire mixture. You point out that the degradation curve provided in your comments for the study (i) shows that although the degradation did not reach a plateau after 28 days, it continued to progress significantly. Hence, you express your opinion that the study (i) allows to conclude on the total mineralisation of the test substance, which you claim to correspond to the Substance.

88 ECHA understands that you argue that the shape of the degradation curve is a sufficient basis to support that all constituents of the substances would show similar degradation kinetics. However, you provide no supporting evidence as to why this information alone can allow excluding that none of the constituent of the substance would fail to meet the ready biodegradability criteria. In the absence of such information, you have not demonstrated that the structural similarity of the constituents of the Substance is such that a single ready biodegradability study is sufficient to inform on the degradation potential of the Substance as a whole.

89 Therefore, the provided studies do not provide unequivocal conclusion that all constituents of the corresponding substances can safely be regarded as readily biodegradable.

5.2.3. (Q)SAR results (ii) are not sufficient to fulfil the information requirement under Annex VII, Section 9.2.1.1.

90 Guidance on IRs and CSA, Section R.7.9.5.1. specifies that (Q)SARs for predicting ready biodegradation are not yet sufficiently accurate to predict rapid degradation. 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.

91 Your dossier provides a (Q)SAR prediction. You have used this information as supporting information to conclude that the Substance is readily biodegradable. As explained above, (Q)SARs predictions can be used as supporting evidence of that the substance is not rapidly degradable. Therefore, this information does not fulfil the information requirement and your adaptation is rejected.

5.2.4. Read-across adaptation rejected for study (iii)

92 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.

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

5.3. Study design and test specifications

94 For the reasons provided above, testing on the Substance as a whole does not fulfil the information requirement. For the generation of information on ready biodegradability, you must consider the level of information required for the purposes of classification and labelling and, if applicable to your registration, the PBT/vPvB assessment and the exposure assessment/risk characterisation. In order to conclude on which of constituents of the

Substance are and which are not readily biodegradable, you may have to consider conducting more than one study using selected individual constituents and/or fractions. If you choose to test one (or more) fraction(s) of the Substance, you must provide a justification that their constituents within chosen fraction(s) are similar enough so that similar degradation kinetics can be assumed. If you decide to conduct a single study in order to prove that all constituents of the Substance are readily biodegradable, you must provide a justification that the selected constituent/fraction can be considered a reasonable worst-case for the Substance as a whole in terms of degradation kinetics.

95 Justification for selection of relevant constituent and/or fractions for the testing, must consider degradation kinetics of constituents of the Substance based, as minimum, on the similarity/differences of the chemical structures and the physico-chemical properties of constituents of the Substance. For that purpose, tools and approaches mentioned in Guidance on IRs and CSA, Sections R.7b and R.11 should be considered.

96 In your comments on the draft decision, you propose to perform an enhanced biodegradation screening study according to OECD TG 301, with extended test duration of up to 60 days. You indicate that you will perform the requested study with components of the Substance if there is still concern of the degradability of the Substance. In this context, you request ECHA to provide more precise information on how the ready biodegradation study/ies with individual components is/are supposed to be performed. You state your concern on the resources needed to obtain individual components of the Substance, as well as, technical aspects of separating and analysing them.

97 ECHA takes note of your intention to conduct an enhanced (60 days) biodegradation screening study on the Substance. However, it remains unclear how such study, if conducted on the Substance as a whole, would resolve the issue identified under Section 5.2.2 above.

98 With regard to the selection of relevant constituent(s)/fraction(s) to conduct the test(s), you are advised to refer to in this section and in the Appendix 4, Section 2.1. below, and references therein. You may choose to test certain fraction(s) of the representative constituent(s) as a reasonable worst-case, or you may provide additional information to prove that all the constituents are structurally similar enough so it may be anticipated that they have similar degradation kinetics in the conditions of the study. In any case, you must provide a justification of the choice of the test material(s) and the test method(s).

99 More generally, you remain responsible for justifying how the information you intend to generate could be used to fulfil or adapt the standard information requirement. You also remain responsible for complying with this decision by the set deadline.

Reasons related to the information under Annex VIII of REACH

6. *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.

6.1. Information provided

101 You have provided:

(i) an *in vitro* cytogenicity study in mammalian cells (2009) with the Substance.

6.2. Assessment of the information provided

6.2.1. Test material in study (i) not representative of the Substance

102 As explained in Section 0.1., the test material in study (i) is not representative of the Substance. In addition, ECHA identified the endpoint-specific issue addressed below.

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

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

a) the maximum concentration tested induces 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 corresponds to 10 mM, 2 mg/mL or 2 µL/mL, whichever is the lowest;

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

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

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

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

104 In study (i), described as an in vitro chromosome aberration study in mammalian cells, you did not report:

a) if the maximum tested concentration did induce 55+5% of cytotoxicity compared to the negative control, and if it did induce the precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL;
b) the number of metaphases scored is not reported;
c) if the positive control data induced responses compatible with those generated in the historical positive control database;
d) the negative controls did not show a response within the historical control range of the laboratory;
e) data on the cytotoxicity and/or the frequency of cells with structural

chromosomal aberration(s) for the treated and control cultures were not reported.

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

106 Therefore, the information requirement is not fulfilled.

107 In your comments on the draft decision, you acknowledge several of the issues identified above. You disagree with ECHA's assessment and consider that an "*in vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)*" is not necessary, without providing a justification. ECHA notes that your comments on the draft decision do not include new information that address the deficiencies identified above. You remain responsible for complying with this decision by the set deadline.

6.3. Specification of the study design

108 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).

6.3.1. Assessment of aneugenicity potential

109 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.

110 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)).

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

111 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.

7.1. Information provided

[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)

112 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) a short-term repeated dose toxicity study (1985) with the source substance diundecyl phthalate, EC 222-884-9;

(ii) a short-term repeated dose toxicity study (1993) with the source substance diundecyl phthalate, EC 222-884-9.

7.2. Assessment of the information provided

7.2.1. Read-across adaptation rejected (i and ii)

113 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. In addition, ECHA identified endpoint-specific issue addressed below.

7.2.1.1. The provided studies do not meet the specifications of the test guidelines

114 To fulfil the information requirement, a study must comply with the OECD TG 407 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the exposure duration is at least 28 days;
b) clinical and functional observations are made, which include body weight and food/water consumption measurements, haematology and clinical biochemistry, and gross necropsy and histopathology of the organs listed in OECD TG 407.

115 In the studies submitted:

a) the exposure duration was only 21 days (i and ii);
b) the following were not assessed/described: clinical and functional observations (ii); body weight and food/water consumption measurements; haematology (i and ii) and clinical biochemistry (ii); as well as gross necropsy and histopathology of the organs listed in the OECD TG 407 at the end of the study (in i only liver, testes and kidneys are described, while in ii only results in testes are described).

116 The information provided does not cover the specification(s) required by the OECD TG 407.

117 Therefore, the information requirement is not fulfilled.

118 In your comments on the draft decision, you acknowledge that "*the documentation to support the adaptation doesn't fulfil the current guidance on the subject - the Read-across assessment framework (RAAF) of March 2017 and RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB) of March 2017*." As already addressed under '0.2.3 Conclusion on the read-across approach', you propose a strategy to improve your adaptation under Annex XI, Section 1.5. (grouping of substances and read-across approach). However, as this strategy relies essentially on data, which is yet to be generated, no assessment can currently be made by ECHA. You remain responsible for complying with this decision by the set deadline.

7.3. Specification of the study design

119 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.

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

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

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

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

123 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.

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

125 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 8 in case the 90-day study is not requested in the adopted decision.

Reasons related to the information under Annex IX of REACH

8. Sub-chronic toxicity study (90 days)

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

8.1. Information provided

127 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 substance:

(i) a sub-chronic toxicity study (1993) with the source substance phthalic acid, di-n-octyl, n-decyl ester (DODP), EC 275-809-7.

8.2. Assessment of the information provided

8.2.1. Read-across adaptation rejected

128 As explained in Section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

8.2.1.1. Source study not adequate for the information requirement

129 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 408. Therefore, the following specifications must be met:

a) clinical signs are observed daily and functional observations (i.e. sensory activity, grip strength and motor activity assessments) are made during week 11 or later;

b) the oestrus cycle in females is examined at necropsy;

c) terminal organ and body weights are measured;

d) full histopathology is performed as specified in the test guideline.

130 In study (i) described as a a sub-chronic toxicity study:

a) The following clinical signs and functional aspects were not assessed: neurobehavioural examination, circulating thyroid hormones (T4, T3, TSH);

b) oestrus cyclicity was not assessed;

c) terminal organ weights and organ/body weight ratios were not recorded;

d) the following histopathology items were not studied: adrenals, pituitary, small and large intestines, gall bladder, skeletal muscle, bone, and bone marrow.

131 The information provided does not cover the specification(s) required by the OECD TG 408.

132 Based on the above, the study does not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 408 and this study is not an adequate basis for your read-across predictions.

133 In your comments on the draft decision, you acknowledge the issues identified above. You state your intent to "*re-evaluate the existing read-across approach*". As already addressed under '0.2.3 Conclusion on the read-across approach', you propose a strategy to improve your adaptation under Annex XI, Section 1.5. (grouping of substances and read-across approach). However, as this strategy relies essentially on data, which is yet to be generated, no assessment can currently be made by ECHA. You remain responsible for complying with this decision by the set deadline.

8.3. Specification of the study design

134 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.

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

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

9. Pre-natal developmental toxicity study in one species

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

9.1. Information provided

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

(i) a pre-natal developmental toxicity study in rats (1996) with the source substance 1,2- benzenedicarboxylic acid, di-C6-10-alkyl esters – L6-10P, EC 271-094-0;

(ii) a pre-natal developmental toxicity study in rats (1999) with the source substance 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, EC 271-085-1;

(iii) a pre-natal developmental toxicity study in rats (2013) with the source substance Diundecyl phthalate, EC 222-884-9.

9.2. Assessment of the information provided

139 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.

140 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.

141 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.

9.2.1. Lack of documentation justifying the weight of evidence adaptation

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

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

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

145 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex IX includes similar information that is produced by the OECD TG 414 on one species. The following aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

146 The studies (i, ii and iii) may provide relevant information on 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

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

9.2.2. Read-across adaptation rejected

148 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.

149 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.

9.3. Conclusion

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

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

152 In your comments on the draft decision, you state: "*weight of evidence approach needs to be critically re-evaluated. This includes the identification of adequate analogue substances and may also require the conduct of appropriate bridging studies (e.g. OECD TG 407, OECD TG 421) for the substance as well as relevant analogue substances within the group of High Molecular Weight Phthalates (HMWP)*" and "*before conducting any new studies in vertebrate animals, the Registrants will first re-evaluate and improve the existing read-across approach*". This strategy relies essentially on data, which is yet to be generated, therefore no assessment can currently be made by ECHA. You remain responsible for complying with this decision by the set deadline.

9.4. Specification of the study design

153 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species.

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

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

10. Long-term toxicity testing on aquatic invertebrates

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

10.1. Information provided

157 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) a non testing guideline long-term toxicity study on Daphnia magna (1984), with the source substance diundecyl benzene-1,2-dicarboxylate, EC 222-884-9;

(ii) a long-term toxicity study on Daphnia magna (1998), performed according to OECD TG 202 (1984) with the source substance diundecyl benzene-1,2-dicarboxylate, EC 222-884-9;

(iii) a non testing guideline long-term toxicity study on Daphnia magna (1997), with the source substance diundecyl benzene-1,2-dicarboxylate, EC 222-884-9.

158 In the 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.

10.2. Assessment of the information provided

10.2.1. Read-across adaptation rejected

159 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. In addition, ECHA identified endpoint specific issue(s) addressed below.

10.2.1.1. Inadequate or unreliable studies (i), (ii) and (iii) on the source substance(s)

160 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 211, and meet the specifications of OECD GD 23 if the substance is difficult to test. The source substances are difficult to test due to their low water solubility. Therefore, the following specifications must be met:

Reporting of the methodology and results

a) the test design is reported (*e.g.* semi-static or flow-through, number of replicates, number of parents per replicate);

b) the test procedure is reported (*e.g.* loading in number of *Daphnia* per litre, test medium composition);

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

d) water quality monitoring within the test vessels (*i.e.* pH, temperature and dissolved oxygen concentration, and TOC and/or COD and hardness where applicable) is reported;

e) the full record of the daily production of living offspring during the test [by each parent animal/in each replicate is provided;

f) the number of deaths among the parent animals (if any) and the day on which they occurred is reported;

g) as explained above, the tested analogue substances are 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.

161 In the studies (i), (ii) and (iii)*:*

Reporting of the methodology and results

a) on the test design for study (iii), you have not specified the test type (e.g. static or flow-through), number of replicates, number of parents per replicate;

b) on the test procedure for study (iii), you have not specified loading in number of Daphnia per litre, test medium composition;

c) the nominal test concentrations and the results of all analyses to determine the concentration of the test substance in the test vessels are not reported for study (ii) and (iii);

d) water quality monitoring within the test vessels (pH, temperature and dissolved oxygen concentration, and TOC and/or COD and hardness) is not reported for study (iii);

e) the full record of the daily production of living offspring during the test by each parent animal is not provided for any of the studies (i), (ii) or (iii);

f) the number of deaths among the parent animals and the day on which they occurred is not reported for any of the studies (i), (ii) or (iii);

g) The tested analogue substances are difficult to test, and you have not provided the information listed above for any of the studies.

162 Based on the above, the reporting of the studies (i), (ii) and (iii) are not sufficient to conduct an independent assessment of its reliability. More specifically, as you have not provided the information listed above under points (a) to (g), ECHA is not in a position to assess whether these tests were conducted under conditions that are consistent with the test guideline specification, whether the validity criteria were met and to assess the interpretation of the study results.

163 On this basis, the specification(s) of OECD TG 211 are not met.

164 In your comments to the draft decision, you point out that the studies were conducted in 1980s and 1990s, according to the test guidelines in force at the time. You acknowledge that the study requirements have changed significantly since then, especially regarding required detail of reporting and the concept of testing poorly soluble substances. Nevertheless, you argue that a weight-of-evidence approach could still be applied, despite the deficiencies of the individual sources of information, since all three sources of information point towards same results (i.e. no effect above waster solubility).

10.2.2. Weight of evidence adaptation rejected

165 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.

166 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.

167 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.

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

169 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.

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

171 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VII, Section 9.1.2. includes similar information that is produced by the OECD TG 211. OECD TG 211 requires the study to investigate the following key elements:

1) the reproductive output of *Daphnia* sp. expressed as the total number of living offspring produced at the end of the test, and
2) the survival of the parent animals during the test, and
3) the time to production of the first brood.

172 The source of information (i) provides NOEC based on the mortality of the parent animals and reproduction. The source of information (ii) provides LC50 and NOEC based on the mortality of the parent animals. The source of information (iii) provides NOEC and LC50 based on the survival / reproduction.

173 Thus, the source of information (i) and (iii) may provide information on the key elements (1) and/or (2), whereas the sources of information (ii) may provide information on the key element (2). However, it is not possible to verify this, as you did not specify on what basis the LC50/NOEC are derived, nor provided raw data on parental mortality or reproductive

output for the sources of information. None of the source of information provide information on the key parameter (3).

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

10.2.2.1. Reliability of the sources of information (i), (ii) and (iii)

175 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. Thus, you have not established that the information on the analogue substances used in the sources of information (i)-(iii) can reliably contribute to your weight of evidence adaptation.

176 In addition, the reliability of the source of information (i), (ii) and (iii) is also affected by the same issue as identified in the section 10.2.1.1. above.

177 Therefore, sources of information (i)-(iii) cannot be considered a reliable sources of information that could contribute to the conclusion on this key parameter investigated by the required study.

10.2.2.2. Conclusion

178 As a conclusion, the sources of information as indicated above, provide relevant information on the long-term toxicity to aquatic invertebrate. However, the reliability of this information is severely impacted by the issues listed above. 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 211 study.

179 The information provided in your comments does not change the assessment. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

10.3. Study design and test specifications

180 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 4.

Reasons related to the information under Annex X of REACH

11. Pre-natal developmental toxicity study in a second species

181 Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is an information requirement under Annex X, Section 8.7.2.

11.1. Information provided

182 You have not submitted any information for this requirement.

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

184 In your comments on the draft decision, you do not agree to perform the requested study. To support your position, you provide the following statement: "*no gain in information is expected when testing the second species*" and refer to two studies ([redacted], 2019 and [redacted], 2008) which, according to you, demonstrate respectively that rat and rabbit "*do not differ in sensitivity to developmental effects*" and "*in general were comparably sensitive towards chemicals with respect to developmental toxicity*". In the comments to the draft decision, you state further that: "*pre-natal developmental toxicity study in a second species will result in unnecessary death of animals, being against the best interest of animal welfare and therefore the Registrant asks that this request will not be included in the final decision*". In addition, you argue that "*data obtained to address request 2 (OECD 414 in the rat) must be generated before a decision on the necessity of a study in a second species can be made*" and refer to the adaptation possibility under Annex IX, Section 8.7.2, Column 2: "*The study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data.*"

185 However, Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is an information requirement under Annex X, Section 8.7.2. Taking into consideration the data currently in your dossier, none of the statements listed above can be used as valid adaptations under REACH. Therefore, you have not demonstrated that this information can be omitted. You remain responsible for complying with this decision by the set deadline.

11.2. Specification of the study design

186 A PNDT study according to the test method OECD TG 414 should be performed in rabbit or rat as preferred second species, depending on the species tested in the first PNDT study (request 9 in this decision).

187 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex X, Section 8.7.2., Column 1).

188 Based on the above, the study must be conducted in rabbits or rats with oral administration of the Substance.

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 Bioaccumulation in aquatic species, preferably fish (Annex IX, Section 9.3.2.) and simulation testing (Annex IX, Section 9.2) are not addressed in this decision. This is because the results from the ready biodegradability is needed to conclude whether the Substance or relevant constituent(s)/fraction(s) of the Substance is (are) P/vP and to decide whether a bioaccumulation study and simulation testing(s) are needed. In such case, the results of the requested ready biodegradability study will also inform on the most relevant test material to conduct the bioaccumulation and simulation studies.

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 5 and by 12 months for all other information requests to take into account currently longer lead times in contract research organisations. ECHA has also notified draft decisions to the registrant of other substances belonging to the category you have formed.

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.

In your comments to the draft decision you request an extension of the deadline from 36 to 51 months based on the following reasons:

- Limited CRO capacity as supported by a CRO letter. The schedule provided by the CRO indicates that the OECD TG 414 in a second species would be completed within 46 months.

- You also consider that 5 extra months are need for "*IUCLID update + revision of read-across justification*", following the completion of the OECD TG 414 study in a second species.

ECHA acknowledges the additional time needed to complete testing due to anticipated delays posed by an appropriate laboratory. The evidence you provided supports extending the deadline to 46 months, which includes completion of the PNDT study in a second species. The timeline set in this decision allows for generating the standard information requirements covered by this decision. In case you decide to submit an adaptation instead of the requested study(ies), it remains your responsibility to provide a compliant adaptation by the set deadline.

On this basis, and based on the documentary evidence provided, ECHA has agreed with your request for a deadline extension and has extended the deadline to 46 months.

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

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

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

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

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

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

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

(1) Selection of the Test material(s)

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

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

(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 the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as

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

far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,
- The reported composition must also include other parameters relevant for the property to be tested, in this case the distribution of alkyl chain length and information on the branching of alkyl side carbon chain (i.e. isomeric composition).

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

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

2. General recommendations for conducting and reporting new tests

2.1. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in Guidance on IRs & CSA, Section R.11.4.2.2, you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesize its relevant constituents and/or fractions.

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