~~Confidential~~

Helsinki, 11 October 2023

Addressee
Registrant of C1012phthalate as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
04/08/2015

Registered substance subject to this decision ("the Substance")
Substance name: bis(decyl and/or dodecyl) benzene-1,2-dicarboxylate
EC number/List number: 931-251-2

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit information under requests 1 and 6 below by ***18 October 2024*** and all other information listed below 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. Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105/OECD GD 29)

2. 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

3. Only if the information requested under request 1 shows the Substance is not poorly water soluble (water solubility > 1 mg/L), Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

4. Only if the information requested under request 1 shows the Substance is poorly water soluble (water solubility < 1 mg/L), Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2)

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

6. 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

7. 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

8. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490)

9. 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 11 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

10. Only if the information requested under request 1 shows the Substance is not poorly water soluble (water solubility > 1 mg/L), 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

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

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

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

14. Long-term toxicity on terrestrial invertebrates also requested below (triggered by Annex IX, Section 9.4.1., column 2)

15. Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: EU C.21./OECD TG 216)

16. Long-term toxicity testing on terrestrial plants also requested below (triggered by Annex IX, Section 9.4.3., column 2)

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

17. 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 or rat)

18. Long-term toxicity testing on terrestrial invertebrates (Annex X, Section 9.4.4.; test method: EU C.33/OECD TG 222 or EU C.32/OECD TG 220)

19. Long-term toxicity on terrestrial plants (Annex X, Section 9.4.6.; test method: EU C.31/OECD TG 208 with at least six species tested or ISO 22030)

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

Information required depends on your tonnage band

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

In the requests above, the same study has been requested under different Annexes. This is because some information requirements may be triggered at lower tonnage band(s). In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band(s). For the highest tonnage band, the reasons why the standard information requirement is not met and the specification of the study design are provided. Only one study is to be conducted; all registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the others under Article 53 of REACH.

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

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 multi-constituent substance (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 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 the substance.

2 The studies submitted for Water Solubility and In vitro gene mutation study in bacteria 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 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. Assessment of the read-across approach

4 By referring to studies performed on analogue substances, we understand that you intend to adapt the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5.:

- *In vitro* gene mutation in bacterial (Annex VII, Section 8.4.1.)
- *In vitro* micronucleus study (Annex VIII, Section 8.4.2.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)
- Short-term toxicity to fish (Annex VIII, Section 9.1.3.)
- Long-term toxicity to aquatic invertebrates (Annex IX, Section 9.1.5.)

5 In the comments to the draft decision you include a read-across adaptation also for the following information requirement:

- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.)

6 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.

7 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.

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

0.2.1. Predictions for (eco)toxicological and fate properties

9 You do not provide a read-across justification document in IUCLID Section 13 or CSR.

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

- diundecyl phthalate, EC 222-884-9; CAS RN 3648-20-2 ([redacted]);
- diundecyl phthalate, EC 222-884-9; CAS RN 3648-20-2 ([redacted]);
- 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters EC 271-094-0; CAS RN 68515-51-5 ([redacted]);
- 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7; CAS RN 71662-46-9 ([redacted]);
- dioctyl phthalate, EC 271-085-1; CAS 68515-43-5.

11 You do not provide any reasoning for the prediction of (eco)toxicological and environmental fate properties.

12 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.

13 We have identified the following issues with the predictions of (eco)toxicological and environmental fate properties:

0.2.1.1. Absence of read-across documentation

14 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 include an explanation why the properties of the Substance may be predicted from information on the source substances.

15 You have provided robust study summaries for the studies conducted with other substances than the Substance in order to comply with the REACH information requirements. However, you have not provided documentation to explain why this information is relevant for the Substance and why the properties of the Substance may be predicted from information on the source substances.

16 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substances.

17 In the comments to the draft decision you state that you will prepare a read-across justification document following the criteria of the RAAF to show similarity of the Substance and source substances. You have not provided such justification as part of your comments to the draft decision.

0.2.1.2. Incomplete characterisation of the Substance and source substances

18 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".

19 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.).

20 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.

21 According to the section 1.2 of the technical dossier, the Substance is described as having two different types of composition (type 1 and type 2) and is a multi-constituent substance.

22 The source substances [redacted] and [redacted] are reported to have the same EC and CAS numbers in the dossier. The provided EC and CAS numbers (i.e. EC 222-884-9; CAS RN 3648-20-2) currently corresponds to [redacted], which is a mono-constituent substance. The same EC and CAS numbers had been used previously for [redacted], an UVCB, which now has different EC and CAS numbers.

23 Furthermore, in the dossier, the test material is also reported as "diundecyl phthalate" without acronym or any further information in the studies addressed in the requests 3, 5 and 13. Therefore, it is not possible for ECHA to verify whether the test material corresponds to [redacted] or [redacted].

24 For the source substances, [redacted] and [redacted], you do not provide any further compositional information.

25 In addition, the studies addressed in requests 5, 6, 8, 10 have been conducted with the [redacted] and [redacted] without further information than the CAS and EC numbers and purity. No information has been provided on purity, composition, degree of oligomerisation, carbon chain length, branching, isomerisation.

26 Without adequate 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.

27 In addition, in the absence of composition information on the test material, the identity of the test material and its impurities cannot be assessed, and you have not demonstrated that the test material is representative for the source substance.

28 In the comments to the draft decision you state you will add compositional information on the target and the selected analogue substances to your read-across justification document.

0.2.1.3. Missing supporting information to compare properties of the substances

29 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.).

30 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effects. In this context, relevant, reliable and adequate information allowing to compare the properties of the substances 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 substances.

31 For the source substances, you provide the studies used in the prediction in the registration dossier. Apart from those studies on the source substances, the registration dossier does not include any robust study summaries or descriptions of data for the Substance that would confirm that both substances cause the same type of effects. Also, you have provided no supporting information to support that variation in the composition, carbon chain length, as well as, the branching of the alkyl chain would not impact the prediction.

32 In the absence of such information, you have not established that the Substance and the source substances are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

0.2.1.4. Inadequate or unreliable studies on the source substances

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

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement.
- 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.

34 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the requests 2, 3, 5, 6, 7, 9, 11, 12, and 13. Therefore, no reliable predictions can be made for these information requirements.

35 In the comments to the draft decision you state that "*All studies were conducted under GLP*" and that "*These data further support the read-across approach and allow a side-by-side comparison of the two substances in regard to their toxicological and ecotoxicological properties. The available data also support the robustness of the read-across approach*". Finally, you state that you will prepare a read-across justification document following the criteria of the RAAF to show similarity.

0.2.1. Conclusion on the read-across approach

36 Based on the above, you have not established that relevant properties of the Substance can be predicted from data on the source substances. Your read-across approach under Annex XI, Section 1.5. is rejected.

37 ECHA takes note of your intentions to improve the (eco)toxicological profile of the Substance and your plans to refine your read-across approach. You remain responsible for complying with this decision by the set deadline.

0.3. Assessment of weight of evidence adaptations

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

Pre-natal developmental toxicity (Annex IX, Section 8.7.1)

Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

- Long-term toxicity to aquatic invertebrates (Annex IX, Section 9.1.5.)

39 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.

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

41 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

43 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.

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

0.3.1. Issues for all endpoints

45 All endpoints adapted by applying weight of evidence rely on sources of information on an analogue substance.

46 However, as explained in section 0.2, your read-across approach under Annex XI, Section 1.5. is rejected.

0.3.2. Endpoint-specific issues

47 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. Water solubility

48 Water solubility is an information requirement under Annex VII to REACH (Section 7.7).

1.1. Information provided

49 You have provided an aqueous solubility study (2009), performed according to ASTM E 1148, with the Substance.

1.2. Assessment of the information provided

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

50 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.

1.2.2. The provided study does not meet the specifications of the test guidelines

51 EU test method A.6 and OECD TG 105 describe two methods (the column elution method and the flask method) for conducting the study. The test method must be selected based on a water solubility estimate obtained in a preliminary study. For substances with preliminary water solubility below 10 mg/L the column elution method must be used.

52 You have provided a study performed with a flask method and you report a water solubility 3.9 mg/L. The reported result falls outside of the applicability domain of the flask method.

53 Therefore, the provided information does not fulfil the information requirement.

54 In the comments to the draft decision, you agree to perform the requested study with the column elution method.

1.3. Specification of the study design

55 Considering the properties of the Substance (solubility < 10 mg/L), the column elution described in EU A.6/OECD TG 105 is the most appropriate method to fulfil the information requirement for the Substance.

2. In vitro gene mutation study in bacteria

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

2.1. Information provided

57 You have provided:

(i) an *in vitro* gene mutation study in bacteria (1987) with the Substance;

(ii) an *in vitro* gene mutation study in bacteria (1993) with the Substance;

(iii) an *in vitro* gene mutation study in bacteria (1985) with a 'range of phthalate esters' (set of structurally related phthalic acid esters);

(iv) an *in vitro* gene mutation study in bacteria (1987) with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7;

(v) an *in vitro* gene mutation study in bacteria (1994) with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7;

(vi) an *in vitro* gene mutation study in bacteria (1990) with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7;

(vii) an *in vitro* gene mutation study in bacteria (1987) with the source substance 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0.

2.2. Assessment of the information provided

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

58 As explained in Section 0.1., the test materials in studies (i) and (ii) are not representative of the Substance. In addition, ECHA identified the endpoint-specific issue addressed below.

2.2.2. The provided studies (i) to (vii) do not meet the specifications of the test guidelines

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);

b) the maximum dose tested induces a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose corresponds to 5 mg/plate or 5 µl/plate;

60 In the studies:

2.1. the test was performed with the strains S. typhimurium TA 97, TA 98 and TA 100 (i.e., the strains *S. typhimurium* TA1535, *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 are missing) in studies (i), (iv) and (vii).

the test was performed with the strains S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and TA 1538 (i.e., the strain *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 is missing) in studies (ii), (v) and (vi).

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

c) the maximum dose tested did not induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance and it was less than 5 mg/plate or 5 µl/plate in study (iv);

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

2.1.1. Read-across adaptation rejected

62 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.

63 Therefore, the information requirement is not fulfilled.

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

2.2. Specification of the study design

65 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.

3. Only if the information requested under request 1 shows the Substance is not poorly water soluble (water solubility >1 mg/L): Short-term toxicity testing on aquatic invertebrates

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

3.1. Information provided

67 We understand that you have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence). Your adaptation is based on the following sources of information:

(i) A short-term toxicity to aquatic invertebrates, performed according to EPA OTS 797.1300 (1984), with the source substance diundecyl phthalate, EC 222-884-9;

(ii) A short-term toxicity to aquatic invertebrates, performed according to EU Method C.2 (1994), with the source substance 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0;

(iii) A short-term toxicity to aquatic invertebrates, performed according to EU Method C.2 (1994), with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7;

(iv) A non-guideline short-term toxicity to aquatic invertebrates (1997), with the source substance diundecyl phthalate, EC 222-884-9.

3.2. Assessment of the information provided

3.2.1. Weight of evidence adaptation rejected

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

69 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 202. OECD TG 202 requires the study to investigate the following key element:

- the concentrations of the test material leading to the immobilisation of 50% of daphnids at the end of the test is estimated.

70 The sources of information (i) to (iv) provide relevant information on this key element.

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

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

72 For the reasons explained in the section 0.1, you have not established that the information on the analogue substances used in the sources of information (i)-(iv) can reliably contribute to your weight of evidence adaptation.

73 In addition, the reliability of the source of information (i) to (iv) is also affected by the following issue:

3.2.1.1.1. Inadequate or unreliable sources of information (i), (ii) (iii) and (iv)

74 To fulfil the information requirement, normally a study according to OECD TG 202 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). The substances referred to in studies (i) to (iii) are difficult to test due to their low water solubility. The OECD TG 203 in combination with the OECD GD 23 specifies that:

75 Technical specifications impacting the sensitivity/reliability of the test

a) the test concentrations are below the limit of solubility of the test material in the dilution water;

Reporting of the methodology and results

d) the test design is reported (e.g. test method, number of replicates, number of animals used, age of the animal, nominal concentrations, vehicle used);

e) the test procedure is reported (composition of the test medium);

f) 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;

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

h) 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;

i) 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.

76 The substances referred to in sources of information (i) to (iv) are difficult to test due to their low water solubility. These studies show the following:

Technical specifications impacting the sensitivity/reliability of the test

a) In the source of information (i), you reported that daphnids were "*entrapped on the surface of the test solution which suggests undissolved test material*". This indicates

that test concentrations are above the limit of solubility of the test material in the dilution water.

Reporting of the methodology and results

b) on the test design, you have not provided any of the information listed above for the source of information (iv);

c) on the test procedure, you have not specified particulate matter and total organic carbon (TOC) in the source study (i)-(iii), and none of the parameters are reported in the source of the information (iv);

d) tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported in the source of information (iv);

e) the dissolved oxygen and pH measured at least at the beginning and end of the test is not reported in the source of information (iv);

f) on the analytical method adequate information: For sources of information (ii) and (iii), you have reported that samples were measured by DOC analysis. The method used is not specific enough to detect the test materials, especially considering that they are complex UVCBs with very low aqueous solubility. Furthermore, in the source of information (iii), you also reported that "*It was not clear whether the measured DOC values resulted from the test substance or from dissolved impurities (approx. 1.5%)*". In the source of information (iv), you indicate that the analytical monitoring was performed, however, no additional information, including the specification of the method used, is provided.

g) As explained above, the tested analogue substances are difficult to test.

- For the source of information (i) to (iv), you have not provided an estimate of the saturation concentration of the corresponding test materials in the test medium and no justification that the method used to prepare test solution allowed to reach saturation.

77 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results for the source of information (i). More specifically, the test appears to have been conducted above the limit of the solubility of the test material.
- the reporting of sources of information (i) to (iv) is not sufficient to conduct an independent assessment of its reliability. More specifically, key elements of the study design (source of information (iv)) and of the study procedure (all studies) are missing and therefore it cannot be verified whether these studies were conducted under conditions that are consistent with the OECD TG 202. Also, you have not provided adequate reporting of the study results for source of information (iv). Finally, the test materials have low solubilities and you have not demonstrated that exposure to the test substance was maximized as required by the OECD GD 23 in any of the studies.

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

3.2.1.2. Conclusion on weight of evidence

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

80 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 a study conducted according to the OECD TG 202.

81 Therefore, your adaptation is rejected, and the information requirement is not fulfilled.

82 In the comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

83 ECHA takes note of your intention. In any case, you remain responsible for complying with this decision by the set deadline.

3.3. Study design and test specifications

84 The Substance is difficult to test due to the adsorptive properties (Log K_{ow} of 11). 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.

85 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).

86 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.

4. Only if the information requested under request 1 shows the Substance is poorly water soluble (water solubility < 1 mg/L): Long-term toxicity testing on aquatic invertebrates

87 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.

4.1. Triggering of the information requirement

88 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.

89 You have provided information which indicates that the Substance includes constituents that are poorly water soluble (Log K_{ow} of11). In addition, as explained in the request 1 above, currently there is no reliable information on water solubility of the Substance in the dossier.

90 Therefore, if the information requested under Request 1 shows the Substance is poorly water soluble, information on long-term toxicity on aquatic invertebrates must be provided, instead of the short-term test.

4.2. Information requirement not fulfilled

91 The information provided, its assessment and the specifications of the study design are addressed under request 13.

92 Therefore, the information requirement is not fulfilled.

93 In the comments to the draft decision, you agree to perform the requested study, if the study requested under A.1., shows that the Substance is poorly water soluble (i.e. water solubility <1 mg/L).

4.3. Study design and test specifications

94 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 3 above.

5. Growth inhibition study aquatic plants

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

5.1. Information provided

96 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 aquatic algae (1984) performed according to the method similar or equivalent to OECD TG 201, with the source substance diundecyl phthalate, EC 222-884-9;

(ii) A growth inhibition study on aquatic algae (1997), without specifying the test guideline, with the source substance diundecyl phthalate, EC 222-884-9;

(iii) A growth inhibition study on aquatic algae (1994), performed according to the EU Method C.3, with the source substance 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0;

(iv) A growth inhibition study on aquatic algae (1994), performed according to the EU Method C.3, with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7.

5.2. Assessment of the information provided

5.2.1. Read-across adaptation rejected

97 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 issues addressed below.

5.2.1.1. Inadequate or unreliable studies (i) to (iv) on the source substances

98 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. As already explained under the request 3, the source substances are difficult to test. Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) one of the two alternative growth medium (*i.e.* the OECD or the AAP medium) is used. Any deviations from recommended test media must be described and justified;

b) *for Desmodesmus subspicatus* the initial cell density is 2-5 x10^3 cells/mL cells/mL;

Reporting of the methodology and results

c) the test design is reported (*e.g.*, number of replicates for each concentration and for control, identity and concentration of the vehicle used, number of test concentrations used);

d) the test conditions are reported (*e.g.*, composition of the test medium, test temperature, pH, biomass density at the beginning of the test);

e) 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;

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

g) 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.

h) 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.

99 Information in studies (i) to (iv):

Technical specifications impacting the sensitivity/reliability of the test

a) You indicate that the standard medium was not used in the study (i) and you have not provided a justification as to why you did not use one of the two alternative growth medium of OECD TG 201

b) In the studies (iii) and (iv), the tests were conducted on *Desmodesmus subspicatus* and the initial cell density was $2x10^4$cells/mL;

Reporting of the methodology and results

c) on the test design, you have not specified number of replicates and identity and concentration of the vehicle used in the study (i). In the study (ii), you have not specified number of replicates and test concentrations used.

d) on the test conditions, you have not provided any of the information listed for the study (ii). For the study (i), you have not provided the composition of the test medium and biomass density at the beginning of the test.

e) the method used to determine algal biomass is not reported in the study (ii). You report that algal biomass was determined using in vivo chlorophyll *a* for the study (i) and photometrical measurements at a wavelength of 685 nm for the studies (iii) and (iv). However, you have not reported evidence of correlation between the measured parameter and dry weight or cell numbers over the range of biomass occurring in the tests.

f) tabulated data on the algal biomass determined daily for each treatment group and control are not reported for the studies (i) and (ii).

g) on the analytical method adequate information, the analytical method used in was not specified and the results of the analytically determined exposure concentrations are not provided for the study (ii). For studies (iii) and (iv), as already explained in the request 3, DOC measurement is not an adequate method for analysing the source substances.

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

100 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the initial cell density used in the studies (iii) and (iv) are higher than specified for the species used and it may impact the sensitivity of the test. Furthermore, you have not justified why one of the two alternative growth medium was not used in study (i).
- the reporting of the studies (i)-(iv) is not sufficient to conduct an independent assessment of its reliability. More specifically, as you have not provided the information listed under point c) to h), 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.

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

102 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.

103 Therefore, the information requirement is not fulfilled.

104 In the comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

105 ECHA takes note of your intention. In any case, you remain responsible for complying with this decision by the set deadline.

5.3. Study design and test specifications

106 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 3 above.

6. Ready biodegradability

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

6.1. Information provided

108 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 ready biodegradability study (2010), performed according to the OECD TG 301B, with the source substance diundecyl phthalate ([redacted]), EC 222-884-9;

(ii) a ready biodegradability study (1984), performed according to the method which is equivalent or similar to the US EPA 560/6-82-003, with the source substance diundecyl phthalate, EC 222-884-9;

(iii) a ready biodegradability study (1995), performed according to the EU Method C.4-C, with the source substance 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0;

(iv) a ready biodegradability study (2010), performed according to the EU Method C.4-C, with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7.

6.2. Assessment of the information provided

6.2.1. Read-across adaptation rejected

109 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 issues addressed below.

6.2.1.1. Ready biodegradation tests are normally intended for pure substances

110 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. In this case, the ready biodegradability test must be performed on relevant constituent(s)/fraction(s) of the Substance.

111 Studies (i), (iii) and (iv) are conducted with UVCB substances as a whole.

112 As explained in Section 0.1.1.2., these source substances are complex substances and contain constituents with significant structural differences originating from varying C-chain length and with potential presence of linear and also undefined branched isomers. Therefore, the provided studies do not provide unequivocal conclusion that all constituents of the test materials used in studies (i), (iii) and (iv) can safely be regarded as readily biodegradable.

6.2.1.2. Inadequate or unreliable study (ii) on the source substance

113 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 301 or 310. Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

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

114 However, in study (ii)

Technical specifications impacting the sensitivity/reliability of the test

1. the inoculum was pre-adapted to the test material.

115 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, adapted inoculum was used in the study (ii) and thus it cannot be regarded as ready biodegradability study.

116 On this basis, the specifications of OECD TG 301/310 are not met.

117 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.

118 Therefore, the information requirement is not fulfilled.

119 In your comments to the draft decision, you agree to perform the requested study and explain you intend to test the Substance as a whole. You consider that "*the EPISuite® biodegradation calculations indicated that the didecyl fraction and the didodecyl fraction are readily biodegradable*" and therefore "*the ready biodegradability test on the whole substance is well justified*".

120 ECHA acknowledges your intention. The Substance is defined as a UVCB and includes constituents with varying C-chain length and degree of branching of the alkyl chain. As explained in Section 6.2.1.1., a study on the whole substance is only acceptable if you provide adequate justification that all constituents of the Substance can be expected to show similar degradation kinetics. In that respect, ECHA points out that, as specified in the

Guidance on IRs and CSA, Section R.7.9.5.1., (Q)SARs for predicting ready biodegradation are not yet sufficiently accurate to predict rapid degradation. As such, (Q)SAR predictions can only be used as supporting evidence of that the substance is not rapidly degradable.

121 Furthermore, as this strategy relies on information that has not yet been fully described and justified, as well as, on QSAR predictions which is not available in your comments nor in your registration dossier, no conclusion on the compliance of the proposed testing strategy can be made. You remain responsible for complying with this decision by the set deadline.

6.3. Study design and test specifications

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. The Substance is a complex substance and contains constituents with significant structural differences originating from varying C-chain length and possible presence of linear and also undefined branched isomers. In this case, the ready biodegradability test must be performed on relevant constituent(s)/fraction(s) of the Substance.

122 The Substance and source substances are a complex substance and contains constituents with significant structural differences described above.

123 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.

124 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.

Reasons related to the information under Annex VIII of REACH

7. In vitro micronucleus study

125 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.

7.1. Information provided

126 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* chromosomal aberration study in human lymphocytes (2009), with the source substance diundecyl phthalate, EC 222-884-9;

(ii) an *in vitro* chromosomal aberration study in human lymphocytes (1990), with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7.

7.2. Assessment of the information provided

7.2.1. Read-across adaptation rejected

127 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 issues addressed below.

7.2.1.1. Inadequate or unreliable studies on the source substances

128 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 473 or OECD TG 487. Therefore, the following specifications must be met:

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

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

129 Information in the studies submitted:

a) in study (i) you did not report the number of metaphases (i.e., less than 300 metaphases) scored per concentration;

b) in studies (i) and (ii) you did not report data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures were not reported;

130 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.

131 Therefore, the information requirement is not fulfilled.

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

7.3. Specification of the study design

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

7.3.1. Assessment of aneugenicity potential

134 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.

135 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)).

136 [1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

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

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

8.1. Triggering of the information requirement

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

139 The information for the in vitro gene mutation study in bacteria and for the in vitro cytogenicity study in mammalian cells provided in the dossier are rejected for the reasons provided in requests 2 and 7.

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

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

8.2. Information provided

142 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 mammalian cells (2009), with the source substance diundecyl phthalate, EC 222-884-9;

(ii) an *in vitro* gene mutation study in mammalian cells (1986), with the source substance diundecyl phthalate, EC 222-884-9;

(iii) an *in vitro* gene mutation study in mammalian cells (2000), with a 'range of phthalate esters with alkyl chain length from C1 to C11';

(iv) an *in vitro* gene mutation study in mammalian cells (1990), with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7.

8.3. Assessment of the information provided

8.3.1. Read-across adaptation rejected

143 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.

144 Therefore, the information requirement is not fulfilled.

145 In the comments to the draft decision, you agree to perform the requested study in case of a negative result in the in vitro cytogenicity test.

8.4. Specification of the study design

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

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

147 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.

9.1. Information provided

148 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:

1. a sub-acute toxicity study (1985), with the source substance diundecyl phthalate, EC 222-884-9;

(v) a sub-acute toxicity study (1993), with the source substance diundecyl phthalate, EC 222-884-9;

(vi) a sub-acute toxicity study (1993), with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7.

9.2. Assessment of the information provided

9.2.1. Read-across adaptation rejected

149 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.

9.2.1.1. Inadequate or unreliable studies on the source substances

150 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed/cover an exposure duration comparable to or longer than the one specified 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) testing is performed with at least three dose levels (unless conducted at the limit dose) and with concurrent controls;

b) dosing of the test substance is performed daily for a minimum of 28 days;

c) 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.

151 Information in the studies submitted:

b) study (iii) only two dose levels were described;

i. In studies (i) and (ii) the exposure duration was limited to 21 days;

c) the following were not assessed/described: clinical and functional observations in study (ii); body weight and food/water consumption measurements; haematology in studies (i) and (ii) and clinical biochemistry in study (ii). In addition, gross necropsy and histopathology of the organs listed in the OECD TG 407 at the end of the study are described only in liver, testes and kidneys in study (i) , and in testes in study (ii).

152 Therefore, the study submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameters or cover an exposure duration comparable to or longer than the one specified in the corresponding OECD TG.

153 Therefore, the information requirement is not fulfilled.

9.3. Specification of the study design

154 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.

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

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

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

157 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 11).

158 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.

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

160 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 11; or
- a 28-day study as per the study design described in 9.3 in case the 90-day study is not requested in the adopted decision.

161 In the comments to the draft decision, you agree to conduct a 90-d study on the Substance (see Request 11) and to provide the justification for an adaptation of the short-term toxicity study.

10. Only if the information requested under request 1 shows the Substance is not poorly water soluble (water solubility >1 mg/L): Short-term toxicity testing on fish

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

10.1. Information provided

163 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 toxicity study on fish (1984), performed according to the EPA/660/3-75-009, with the source substance diundecyl phthalate, EC 222-884-9;

(ii) a short-term toxicity study on fish (1983), performed according to the EPA/660/3-75-009, with the source substance diundecyl phthalate, EC 222-884-9;

(iii) a short-term toxicity study on fish (1997), no guideline specified, with the source substance diundecyl phthalate, EC 222-884-9, containing study records for the following test species:

(i) Oncorhynchus mykiss

(ii) Cyprinodon variegatus

(iii)Pimephales promelas

(iv)Lepomis macrochirus

(v) a short-term toxicity study on fish (1984), performed according to an international protocol "EG&G Bionomiccs Method for conducting flow-through toxicity tests with freshwater fish" (1981) and the protocol amendment EG&G/CMA-007B, with the source substance diundecyl phthalate, EC 222-884-9;

(vi) a short-term toxicity study on fish (1983), performed according to the EPA-660/3-75-009 (1975), with the source substance diundecyl phthalate, EC 222-884-9;

(vii) a short-term toxicity study on fish (1994), performed according to the EU Method C.1., with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7.

10.2. Assessment of the information provided

10.2.1. Read-across adaptation rejected

164 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 on the source substance(s)

165 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 203, and meet the specifications of OECD GD 23 if the substance is difficult to test. Therefore, the following specifications must be met:

Reporting of the methodology and results

1. the test design is reported (*e.g.* static, semi-static or flow-through, number of test animals);

d) the test procedure is reported (e.g. composition of the test medium, fish loading);

e) 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;

f) 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.

166 Information in the studies submitted:

Reporting of the methodology and results

1. on the test design, you have not specified any information listed above in the study (iii).

g) on the test procedure, you have not specified:

10.2.1.1. Study (i): fish loading and hardness is not reported. In addition, natural seawater is used but parameters such as TOC/DOC and nitrate are not reported.

10.2.1.2. Studies (ii) and (v): fish loading is not reported. Well water is used but parameters such as TOC/DOC and nitrate are not reported.

10.2.1.3. Study (iii): no information is provided on the test medium composition and fish loading.

10.2.1.4. Study (iv): Well water is used but parameters such as TOC/DOC and nitrate are not reported.

10.2.1.5. Study (vi): drinking water is used parameters such as TOC/DOC is not reported.

h) on the analytical method, adequate information, i.e. the method used and the performance parameters of the method, and the results of the analytically determined exposure concentrations are not provided for the study (iii). For study (vi), you stated that DOC measurements were used. As already explained in the request 3, DOC measurement is not an adequate method for analysing the source substances.

i) you have not provided the information listed above for any of the studies.

167 Based on the above, the reporting of the studies is not sufficient to conduct an independent assessment of their reliability. More specifically, as you have not provided the information listed a)-d), 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 203 and OECD GD 23, and to assess the interpretation of the study results.

168 On this basis, the specifications of OECD TG 203 are not met.

169 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.

170 Therefore, the information requirement is not fulfilled.

171 In the comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

172 ECHA takes note of your intention. In any case, you remain responsible for complying with this decision by the set deadline.

10.3. Study design and test specifications

173 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 3.

Reasons related to the information under Annex IX of REACH

11. Sub-chronic toxicity study (90-day)

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

11.1. Information provided

175 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 sub-acute toxicity study (1993, Report number 1000/2/93), with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7.

11.2. Assessment of the information provided

11.2.1. Read-across adaptation rejected

176 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.

11.2.1.1. Inadequate or unreliable study on the source substance

177 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 408. Therefore, the following specifications must be met:

1. 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;

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

k) terminal organ and body weights are measured;

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

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

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

m) oestrus cyclicity was not assessed;

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

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

179 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 ones specified in the corresponding OECD TG.

180 Therefore, the information requirement is not fulfilled.

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

11.3. Specification of the study design

182 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.

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

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

12. Pre-natal developmental toxicity study in one species

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

12.1. Information provided

186 We understand that you have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence). Your adaptation is based on the following experimental data:

(i) a pre-natal developmental toxicity study in rats (1996, Report number [redacted]), with the source substance 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0;

(ii) a pre-natal developmental toxicity study in rats (1999, Report number [redacted]), with the source substance, dioctyl phthalate, EC 271-085-1.

12.2. Assessment of the information provided

12.2.1. Weight of evidence adaptation rejected

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

188 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.

189 The sources of information (i) and (ii) provide information on pre-natal developmental toxicity, maternal toxicity and maintenance of pregnancy.

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

12.2.1.1. Reliability of the contribution of the information on the analogue substances: Read-across rejected

191 As explained in Section 0.2, you have not established that the information on the analogue substances used in the sources of information (i) and (ii) can reliably contribute to your

weight of evidence adaptation. In addition, the reliability of the source of information (i) and (ii) is also affected by the following issue:

Inadequate or unreliable sources of information (i)

192 Normally a study according to OECD TG 414 must be provided. The specifications of OECD TG 414 include:

the exposure duration is at least from implantation until one day prior to scheduled caesarean section;

a) the dams are examined for histopathology of the thyroid gland, and thyroid hormone measurements;

b) the foetuses are examined for resorptions, and sex ratio in all live rodent foetuses.

193 Information in study (i):

a) the exposure duration was from days 6 to 16 of gestation, *i.e.* 10 days;

b) data on the examination of the dams, including incidence and severity, are missing. In particular, the following investigations are missing: histopathology of the thyroid gland;

c) data on the examination of the foetuses, including incidence and severity, are missing; In particular, the following investigations are missing: resorptions and sex ratio.

194 Therefore, the study (i) submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key specifications and does not cover an exposure duration comparable to or longer than the one specified in the corresponding OECD TG.

- *Conclusion on weight of evidence*

195 As a conclusion , the sources of information (i) and (ii) provide relevant information on prenatal developmental toxicity, maternal toxicity, and maintenance of pregnancy. However, the reliability of sources of information (i) and (ii) is significantly affected by the deficiencies described above.

196 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 OECD TG 414. Therefore, your adaptation is rejected.

197 Therefore, the information requirement is not fulfilled.

198 In the comments to the draft decision, you agree to perform the requested study in rats.

12.1. Specification of the study design

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

200 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).

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

13. Long-term toxicity testing on aquatic invertebrates

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

13.1. Information provided

We understand that you have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence). Your adaptation is based on the following experimental data:

(i) a long-term toxicity study on *daphnia magna* (1998), performed according to OECD TG 202 (1984), with the source substance Diundecyl phthalate, EC 222-884-9;

(ii) a long-term toxicity study on *daphnia magna* (1984), no guideline followed, with the source substance Diundecyl phthalate, EC 222-884-9;

(iii) a long-term toxicity study on *daphnia magna* (1985), no guideline followed, with the source substance Diundecyl phthalate, EC 222-884-9;

(iv) a long-term toxicity study on *daphnia magna, non guideline* (1997), with the source substance Diundecyl phthalate, EC 222-884-9.

13.2. Assessment of the information provided

13.2.1. Weight of evidence adaptation rejected

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

204 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.

205 The source of information (iii) does not provide information on any of the key elements listed above as the effect concentrations are based on immobilisation of Daphnia sp. Therefore, the sources of information (iii) are not relevant.

The source of information (i) provides information on the key element (2). The source of information (ii) provides information on the key elements (1) and (2). The source of information (iv) provides NOEC and LC_{50} based on the survival/reproduction and mortality/ reproduction. Thus, the source of information (iv) may provide information on the key elements (1) and/or (2). However, it is not possible for ECHA to verify this, as you did not specify on what basis the LC50/NOEC are derived, nor provided raw data on the key elements (1), (2), and (3) for the sources of information. None of the source of information provide information on the key parameter 3).

206 In addition, the reliability of these sources of information is significantly affected by the following deficiencies as further explained below.

13.2.1.1. Reliability of the sources of information (i), (ii) and (iv): Read-across rejected

207 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, the reliability of the source of information (i), (ii) and (iv) is also affected by the following issue.

13.2.1.1.1. The reliability provided sources of information (i), (ii) and (iv) cannot be assessed

208 To fulfil the information requirement, normally a study according to OECD TG 211 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). As already in the request 3 above, explained the source substance, diundecyl phthalate (EC 222-884-9) referred in the sources of information (i) to (iv) is difficult to test due to its low water solubility. The specifications of OECD TG 211 and OECD GD 23 include:

Technical specifications impacting the sensitivity/reliability of the test

i. the test concentrations are below the limit of solubility of the test material in the dilution water;

Reporting of the methodology and results

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

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

f) 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.

g) the full record of the daily production of living offspring during the test is provided.

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

i) 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;

j) as explained above, the source 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, and
- 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.

209 Information in sources of information (i), (ii), and (iv):

Technical specifications impacting the sensitivity/reliability of the test

- in the source of information (ii), you report that "*Effect concentrations exceeding solubility of substance in test medium: entrapment in 1st 14 days in 0.028 & 0.059 mg/l groups*", suggesting that the test concentrations were above the limit of solubility of the test material.

Reporting of the methodology and results

k) for the source of information (iv): on the test design, you have not specified any of the information listed above.

l) on the test procedure, you have not specified loading in number of *Daphnia* per litre in any of the sources of information.

m) water quality monitoring within the test vessels is not reported in the sources of information (i) and (iv), and TOC/DOC is not reported in the source of information (ii).

n) the full record of the daily production of living offspring during the test is not provided in any of the sources of information.

o) You have reported the deaths among the parent animals in the control and treatments in the source of information (ii). However, exact days that they occurred are not reported.

p) on the analytical method adequate information, (i.e. the method used and performance parameters of the method) is not reported in the sources of information (i) and (iv). Furthermore, the nominal and measured concentration are not reported in the source of information (iv).

q) you have not provided the information listed above for any of the sources of information.

210 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically for source of information (ii), the test concentrations were above the limit of the solubility of the test material.
- the reporting of source of information (i), (ii) and (iv) is not sufficient to conduct an independent assessment of its reliability. More specifically, key elements of the study design (source of information (iv)) and of the water quality monitoring (all sources of information) are missing and therefore it cannot be verified whether these studies were conducted under conditions that are consistent with the OECD TG 211. Also, you have not provided adequate reporting of the study results for all of the source of information. Finally, the test materials have low solubilities and you have not demonstrated that exposure to the test substance was maximized as required by the OECD GD 23.

211 Therefore, sources of information (i), (ii), and (iv) cannot be considered reliable sources of information that could contribute to the conclusion on this key parameter investigated by the required study.

13.2.2. Conclusion on weight of evidence adaptation

212 As a conclusion, the sources of information (i), (ii) and (iv) as indicated above, provide some relevant information on the long-term toxicity to invertebrates. However, the reliability of the contribution of the information is impacted by the use of information on analogue substance and by methodological deficiencies in the study design and/or in reporting listed above.

213 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 a study conducted according to the OECD TG 211. Therefore, your adaptation is rejected, and the information requirement is not fulfilled.

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

13.3. Study design and test specifications

215 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 3.

14. Long-term toxicity on terrestrial invertebrates

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

14.1. Triggering of the information requirement

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

218 For the reasons explained in the request 6 above, the information requirement on ready biodegradability is not met. Therefore, you have not demonstrated that the Substance is readily biodegradable. In addition, based on the information from your registration dossier, the Substance is considered to have high adsorption potential to soil as you report a log Kow above 5 for the Substance.

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

14.2. Information requirement not fulfilled

220 The information provided, its assessment and the specifications of the study design are addressed under request 18 below.

15. Effects on soil micro-organisms

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

15.1. Information provided

222 You have adapted this information requirement under Annex IX, Section 9.4., Column 2 with the following justification:

223 *"studies of the effects on terrestrial organisms need not be conducted if direct and indirect exposure of the soil compartment is unlikely. It is proposed that testing is waived as, although the substance has a high 35now of 8.70 and a high potential to adsorb to soil, it can be regarded as readily biodegradable indicating that it will not remain in the environment*".

15.2. Assessment of the information provided

224 Under Annex IX, Section 9.4., Column 2, toxicity studies with soil organisms may be omitted if direct and indirect exposure of the soil compartment is unlikely.

225 In the registration dossier you report a number of various industrial, professional and consumer uses of the Substance including use in adhesives and lubricants (outdoor) by professional users and consumers. There is no exposure assessment and risk characterisation reported in the chemical safety report.

226 Based on the uses identified in the registration dossier direct and/or indirect (e.g. for outdoor uses of lubricants etc.), exposure of the soil cannot be ruled out. For instance, ECHA Guidance on IRs and CSA, Section 16 identifies a worst-case release factor of 20% to soil for environmental release category (ERC) 8d which you assigned for use in artist supply. Furthermore, you have not reported any further justification (e.g. exposure assessment for soil compartment) which would support your adaptation on the basis of exposure considerations.

227 Therefore, your adaptation is rejected, and the information requirement is not fulfilled.

228 In the comments to the draft decision, you indicate you intention to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

229 ECHA takes note of your intention. In any case, you remain responsible for complying with this decision by the set deadline.

15.3. *Study design and test specifications*

230 ECHA Guidance R.7.11.3.1. specifies that Soil Microorganisms: Nitrogen Transformation Test (EU C.21/OECD TG 216) is considered suitable for assessing long-term adverse effects on soil microorganisms for most non-agrochemicals.

16. Long-term toxicity on terrestrial plants

231 Short-term toxicity plants is an information requirement under Annex IX to REACH (Section 9.4.3). Long-term toxicity testing must be considered (Section 9.4., column 2), if the substance has a high potential to adsorb to soil or is very persistent.

16.1. Triggering of the information requirement

232 For the reasons already explained under the request 14 above, information on long-term toxicity on plants invertebrates must be provided for the Substance.

16.2. Information requirement not fulfilled

233 The information provided, its assessment and the specifications of the study design are addressed under request 19 below.

Reasons related to the information under Annex X of REACH

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

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

17.1. Information provided

235 You have adapted this information requirement and provided the following justification:

(i) *"The registrant understands that according to Annex X, 8.7.2, column 1 of the REACH Regulation, the pre-natal developmental toxicity 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 according to* **Annex IX, 8.7.2, column 2** *of the REACH Regulation".*

(ii) *"In the absence of any indications of the substance affecting rat development in the pre-natal study, there is no reason to suggest that any effects on development are likely in other species."*

(iii) "A pre-natal developmental toxicity in a second species is scientifically unjustified based on the adequate available data and in terms of ***animal welfare***, noting testing on vertebrate animals for the purposes of Article 25 of the REACH regulation shall be undertaken only as a last resort."

b) Assessment of the information provided

17.1.1. Your justification to omit the study (i), (ii) and (iii) has no legal basis

236 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex X, Section 8.7.2., column 2.

237 The legal provision of Annex IX, Section 8.7.2., column 2 that you refer to is not an adaptation possibility for waiving an experimental study at Annex X. Instead, it lays out the conditions under which a PNDT-study is triggered in a second species, based on (hazardous) effects observed in a PNDT study with the first species at Annex IX.

238 Your substance is registered at Annex X, for which the submission of a PNDT study in a second species is an information requirement.

239 Therefore, you have not demonstrated that this information can be omitted.

240 Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI or Annex X, Section 8.7.2., column 2.

241 Therefore, the information requirement is not fulfilled.

242 From the comments to the draft decision, ECHA understands that you intend to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

243 ECHA takes note of your intention. In any case, you remain responsible for complying with this decision by the set deadline.

17.2. Specification of the study design

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 12 in this decision).

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).

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

18. Long-term toxicity testing on terrestrial invertebrates

244 Long-term toxicity testing on invertebrates is an information requirement under Annex X to REACH (Section 9.4.4.).

18.1. Information provided

245 You have provided no information on long-term toxicity on terrestrial invertebrates. Instead, you have adapted this information under Annex X, Section 9.4., Column 2 with the same justification as already described under the request 15 above.

18.2. Assessment of the information provided

246 For the reasons already explained under the request 15 above, your adaptation is rejected. On this basis, the information requirement is not fulfilled.

247 In the comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

248 ECHA take snot of your intention. IN any case, you remain responsible for complying with this decision by the set deadline whether with the required study or with a valid adaptation.

18.3. Study design

249 ECHA Guidance R.7.11.3.1. specifies that the earthworm reproduction test (OECD TG 222), the Enchytraeid reproduction test (OECD TG 220), and the Collembolan reproduction test (OECD TG 232) are appropriate to cover the information requirement for long-term toxicity testing on terrestrial invertebrates. ECHA is not in a position to determine the most appropriate test protocol since this decision is dependent upon species sensitivity and substance properties. However, when log Kow >5 and log Koc >4, as in this case, the test OECD 232 is not appropriate as the dominant route of exposure for Collembolans is via pore water.

19. Long-term toxicity testing on terrestrial plants

250 Long-term toxicity testing on plants is an information requirement under Annex X to REACH (Section 9.4.6.).

19.1. Information provided

251 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:

1. short-term toxicity to plants, performed according to OECD TG 208, with the source substance 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0;

(i) short-term toxicity to plants, Performed according to OECD TG 208, with the source substance, 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7.

252 In addition, you have adapted this information under Annex X, Section 9.4., Column 2 with the same justification as already described under the request 15 above.

19.2. Assessment of the information provided

19.2.1. Read-across adaptation rejected

253 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.

254 In addition, ECHA identified endpoint specific issues addressed below.

19.2.1.1. Studies cannot be considered adequate for long-term studies.

255 For long-term toxicity testing, ECHA considers six species as the minimum to achieve a reasonably broad selection. Testing must be conducted with species from different families, as a minimum with two monocotyledonous species and four dicotyledonous species, selected according to the criteria indicated in the OECD TG 208.

256 The provided studies (i) and (ii) do not qualify for long-term toxicity testing as only three species (one monocotyledonous species and two dicotyledonous species) were used.

257 Therefore, these studies do not qualify for long-term toxicity test on plants.

19.2.2. Your adaptation based on exposure considerations is rejected.

258 In addition, for the reasons already explained under the request 15 above, your adaptation under Annex X, Section 9.4., Column 2 is rejected.

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

260 In the comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

261 ECHA takes note of your intention. In any case, you remain responsible for complying with this decision by the set deadline.

19.3. Study design and test specifications

262 The Terrestrial Plant Test (test method: OECD TG 208) is appropriate to cover the information requirement for long-term toxicity on terrestrial plants.

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

References

The following documents may have been cited in the decision.

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

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

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

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

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 to conclude on the PBT/vPvB properties of the Substance. 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.

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 requests 1 and 6, and by 12 months for all other information requests to take into account currently longer lead times in contract research organisations.

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

ECHA took into account your comments and did not amend the requests 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 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[2].
(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

(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 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

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

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.

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.