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Helsinki, 11 October 2023

Addressees
Registrants of JS_68515-43-5 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
10/02/2014

Registered substance subject to this decision ("the Substance")
Substance name: 1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters
EC/List number: 271-085-1

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 all the information by ***19 April 2027***.

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

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

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

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

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

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

4. 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.

5. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: 7. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

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

   or in case the sub-chronic toxicity study (90 days) is not requested, Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.; test method: EU B.7./OECD 407) by oral route, in rats

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

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

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

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

9. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit) Click here to select a HH request

The reasons for the requests are explained in Appendix 1.

Information required depends on your tonnage band

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

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.

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

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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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. Assessment of the read-across approach

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2)
- Long-term toxicity to aquatic invertebrates (Annex IX, Section 9.1.5.)

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

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

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

0.1.1. Scope of the grouping of substances (category)

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

6 For the purpose of this decision, the following category members are listed in the read-across justification document:

(1) 1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters, CAS RN 71662-46-9
(2) 1,2-benzenedicarboxylic acid, di-C8-10-alkyl esters, CAS RN 71662-46-9
(3) Decyl nonyl phthalate, CAS RN 96507-76-5
(4) Isononyl undecyl phthalate, CAS RN 96507-82-3
(5) Isoundecyl nonyl phthalate, CAS RN 96507-78-7
(6) Diundecyl phthalate, CAS RN 3648-20-2
(7) Didodecyl phthalate, CAS RN 2432-90-8
(8) 1,2-Benzenedicarboxylic acid, mixed decyl, lauryl and myristyl di esters, CAS RN 90193-92-3

7 You justify the grouping of the substances as: "*1,2-benzenedicarboxylic acids, with side chain esters ranging in carbon chain length from C1 to C13. In addition to carbon chain length, structure will vary depending on the isomeric composition of the alcohol used in their manufacture. Ester side chains may be linear isomers (for example: di-methyl and di-n-heptyl phthalates), branched isomers (for example: diisohexyl phthalate), and/or a combination of benzyl and linear or branched isomers (for example: benzyl butyl phthalate and benzyl C7-C9 branched and linear phthalate)*".

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

- Low molecular weight phthalates produced from alcohols with straight-chain carbon backbones of <C3.

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

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

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

0.1.1.1. Incomplete characterisation of the Substance and the source substances

11 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*".

12 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.).

13 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.

14 Your read-across justification document does not contain any compositional information for the Substance and the source substances. The Substance and the source substances are complex UVCBs. The core structure consists of a cyclic ring structure (i.e., 1,2-benzenedicarboxylic acid) esterified with alcohols of varying carbon chain length that may be linear or branched.

15 However, you have provided no detailed information on the carbon chain length distribution and the isomeric composition of branched constituents for the Substance and the selected category members.

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

0.1.2. Predictions for (eco)toxicological properties

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

1. 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0;
2. 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7;
3. diundecyl phthalate, EC 222-884-9;
4. diundecyl phthalate, EC 287-401-6;

5. phthalsaeure-di-C9-C11-alkyl ester, EC 601-037-0;
6. 1,2-Benzenedicarboxylic acid, di-C9-11-alkyl esters, EC 272-012-6;
7. 1,2-Benzenedicarboxylic acid di-9-11 branched and linear alkyl ester, No EC nor CAS RN provided;
8. 1,2-Benzenedicarboxylic acid, mixed decyl and lauryl and myristyl diesters, EC 290-598-1;
9. 1,2-Benzenedicarboxylic acid, mixed decyl and lauryl and myristyl diesters, EC 290-598-1.

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

- "*All the substances exhibit similar physico-chemical properties, in particular low water solubility and high octanol-water partition coefficient*".
- "*Due to structural similarities, comparable physical/chemical properties the toxicokinetic profile of the registered substance and the potential structural analogue substances are also expected to be comparable in terms of physiological absorption, distribution, metabolism and excretion processes*".
- "*Metabolism of any absorbed phthalate di-ester commences with rapid hydrolysis to the mono-ester which is then followed by further hydrolysis and/or oxidation and glucuronidation*".
- "*The data available on environmental effects indicate that all the substances exhibit similar aquatic toxicity, this limited by their low water solubility*".
- "*The presence of a common structure and functional group (the phthalate ester moiety) that is responsible for the observed toxicological and ecotoxicological effects, together with the observed similarities in effect of a number of substances across a broad range of end-points, is regarded as sufficiently robust to justify the use of read-across to fill the information data gaps of the target substance*".

19 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.

20 We have identified the following issues with the predictions of (eco)toxicological properties:

0.1.2.1. Insufficient data density

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

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

23 You have provided:

- *in vitro* chromosome aberration studies in mammalian cells for two category members (source substances EC 222-884-9 and EC 275-809-7);
- *in vitro* gene mutation study in mammalian cells for two category members (source substances EC 222-884-9 and EC 275-809-7);
- a sub-chronic repeated dose toxicity data on for one category member (source substances EC 275-809-7);
- growth inhibition studies on aquatic plants with three category members (EC 601-037-0, EC 271-094-0, and EC 275-012-6);
- long-term aquatic invertebrate studies on two category members (EC 272-012-6

and 287-401-6).

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

0.1.2.2. Missing supporting information to compare the properties of the substances

25 Annex XI, Section 1.5 requires that whenever read-across is used "supporting information to scientifically justify such explanation for prediction of properties" must be provided. 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 substances (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

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

27 For the source substances, you provide the studies used in the prediction in the registration dossier. Apart from studies on the source substances, your read-across justification or the registration dossier does not include any robust study summaries or descriptions of data for the Substance that would confirm that 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.

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

29 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.

0.1.2.3. Inadequate or unreliable studies on the source substances

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

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

31 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the requests 1, 2, 5, 6, 7, 8, and 9. Therefore, no reliable predictions can be made for these information requirements.

0.1.3. Conclusion on the read-across approach

32 For the reasons 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.

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

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

0.2. Assessment of weight of evidence adaptations

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity in mammalian cells (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2)
- Long-term toxicity to aquatic invertebrates (Annex IX, Section 9.1.5.)

36 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.

37 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.

38 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.

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

40 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.

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

0.2.1. Issues for all endpoints

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

43 However, as explained in section 0.1, your read-across approach under Annex XI, Section 1.5. is rejected.

0.2.2. Endpoint-specific issues

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

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

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

1.1. Information provided

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

(i) an *in vitro* gene mutation study in bacteria (1983/2000) with the source substance 1,2-Benzenedicarboxylic acid di-9-11 branched and linear alkyl ester, no EC, CAS provided;
(ii) an *in vitro* gene mutation study in bacteria (1985) with the source substance diundecyl phthalate, EC 222-884-9; diundecyl phthalate, EC 287-401-6;
(iii) 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 (L6-10P-Sasol);
(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 (L8-10P-Sasol-1);
(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 (L8-10P-Sasol-2);
(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 (L8-10P-Sasol-3);
(vii) an *in vitro* gene mutation study in bacteria (1987) with the source substance 1,2-Benzenedicarboxylic acid, mixed decyl and lauryl and myristyl diesters, EC 290-598-1 (L10-12-14P-Sasol-1); and
(viii) an *in vitro* gene mutation study in bacteria (1993) with the source substance 1,2-Benzenedicarboxylic acid, mixed decyl and lauryl and myristyl diesters, EC 290-598-1 (L10-12-14P- Sasol-2).

1.2. Assessment of the information provided

1.2.1. Weight of evidence adaptation rejected

47 As explained under Section 0.2 the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

48 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.1. at Annex VII includes similar information that is produced by the OECD TG 471 with a design specified in this decision. OECD TG 471 requires the the study to investigate the following key element:

- detection and quantification of gene mutation (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies. The sources of information (i), to (viii) investigate the above mentioned key parameter.

49 A level of information on these aspects similar to that obtained from an in vitro gene mutation test in bacteria (OECD TG 471) is required.

50 The sources of information (i) to (viii) provide relevant information on this key investigation.

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

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

52 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) to (viii) can reliably contribute to your weight of evidence adaptation.

53 In addition, the reliability of the source of information (i) to (viii) is also affected by the following significant deficiencies:

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

54 To fulfil the information requirement, normally a study according to OECD TG 471 (2020) must be provided. The OECD TG 471 specifies that:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).
b) Triplicate plating must be used at each dose level.
c) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
d) The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.
e) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

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

a) The reported data for all the studies you have provided did not include results for the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). In addition, for the studies (iii) and (vii) the strain TA1535 is also missing.
b) The reported data for the study (i) you have provided did not include triplicate plating at each dose level.
c) For the studies (i) and (viii) you have not provided information if the positive control produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
d) For the studies (ii), (v) and (vi) you did not provide information on whether the negative control with a number of revertant colonies per plate is inside the historical control range of the laboratory.
e) The reported data for the studies (i), (ii), and (iii) you have provided did not include data on the number of revertant colonies per plate for the treated doses and the controls.

56 In summary, all the sources of information (i) to (viii) have a critical reliability issue with regard to not having data on the required fifth strain. In addition, the sources of information (i) to (viii) have other significant reliability issues and cannot therefore contribute to the conclusion on the potential of the Substance to cause gene mutations in bacterial cells.

57 In the absence of such information on such critical aspects of the specifications of the provided studies, ECHA cannot evaluate the reliability of the conclusions on the frequency of gene mutation in bacteria.

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

1.2.1.2. Conclusion

59 As a conclusion, the sources of information as indicated above, provide information on in vitro gene mutation study in bacteria. However, the reliability of this information is severely impacted by the issues listed above.

60 Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 471 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

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

1.3. Specification of the study design

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

2. Growth inhibition study aquatic plants

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

2.1. Information provided

64 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) Growth inhibition study on algae (1988)with the source substance phthalsaeure-di-C9-C11-alkyl ester, EC 601-037-0 ([redacted])

(ii) Growth inhibition study on algae (1994) with the source 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters, EC 271-094-0 ([redacted])

(iii) Growth inhibition study on algae (1994) with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7 ([redacted])

2.2. Assessment of the information provided

2.2.1. Weight of evidence adaptation rejected

65 As explained under Section 0.2 the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

- the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test are estimated.

67 The sources of information (i) to (iii) provide relevant information on this key element.

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

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

69 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)-(iii) can reliably contribute to your weight of evidence adaptation.

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

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

71 To fulfil the information requirement, normally a study according to OECD TG 201 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 201 in combination with the OECD GD 23 specifies that:

72 *Technical specifications impacting the sensitivity/reliability of the test*

a) *for Desmodesmus subspicatus* the initial cell density is 5 x 10^3-10^4 cells/mL.

73 *Characterisation of exposure*

b) the test media prepared specifically for analysis of exposure concentrations during the test is treated identically to those used for testing (i.e. inoculated with algae and incubated under identical conditions).

74 *Reporting of the methodology and results*

c) the test design and conditions are reported (number of replicates, composition of the test medium, concentration of the vehicle, test temperature, pH, biomass density at the beginning of the test).

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

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

f) 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 study,
- a description of the methods used to prepare stock and test solutions,
- if the test material is tested at the saturation concentration, evidence that all reasonable efforts have been taken to achieve a saturation

concentration.

75 In the source of information (i) to (iii):

76 *Technical specifications impacting the sensitivity/reliability of the test*

a) In sources of information (ii) and (iii), the test was conducted on *Desmodesmus subspicatus* and the initial cell density was $2x10^4$ cells/mL for both studies.

77 *Characterisation of exposure*

b) For sources of information (ii) and (iii), the test media prepared specifically for analysis of exposure concentrations was not inoculated with algae.

78 *Reporting of the methodology and results*

c) You did not report adequate information on the test design and conditions for the source information (i), and in particular, the number of replicates, the composition of the test medium, concentration of the vehicle, the test temperature, pH and the biomass density at the beginning of the test.

d) For source of information (i), the method used to determine algal biomass is not reported. For sources of information (ii) and (iii), you report that algal biomass was determined photometrically at wavelength of 685 nm. 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 test.

e) For none of the sources of information, tabulated data on the algal biomass determined daily for each treatment group and control are not reported. Furthermore, for source of information (ii), you seem to have reported the data and conclusion of the source of information (iii), rather than those from the sources of information (ii).

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

- For the source of information (i), you have performed a test at a single concentration but you neither specify whether analytical monitoring was performed nor reported measured concentrations. For sources of information (ii) and (iii), You have reported that samples were analysed for DOC with a TOC-500-infrared analyser. 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%)*".
- For the source of information (i) to (iii), 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.

79 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the studies results. More specifically, initial biomass was too high in studies (ii) and (iii) which may have reduced the sensitivity of these studies. Furthermore, for any of these studies you have provided reliable information to justify that test organisms were adequately exposed to the test material over the exposure period (either because no analytical monitoring is reported, the test medium was not inoculated with algae or the analytical method had insufficient specificity and sensitivity). Furthermore, 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.

- the reporting of the studies is not sufficient to conduct an independent assessment of their reliability. More specifically, you have not provided adequate information to demonstrate that study (i) was conducted under conditions that are consistent with the OECD TG 201. The method used to estimate biomass is also unclear for all sources of information (i) to (iii). Finally, in the absence of tabulated biomass data, it is not possible to verify if these sources of information met the validity criteria of the OECD TG 201 and to assess the interpretation of the results.

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

2.2.1.2. Conclusion

81 As a conclusion, the sources of information as indicated above, provide relevant information on the toxicity to algae. However, the reliability of this information is severely impacted by the issues listed above.

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

83 In your comment to the draft decision, you acknowledge that there are flaws in the provided sources of information (i)-(iii). You explain that these are due to the fact that the selected analogues substances are difficult to test and how studies were used to be performed at the time of the testing (i.e., 1990s). You argue that a weight-of-evidence approach could still be applied, despite the deficiencies of the individual sources of information as:

- for all three sources of information the EC_{50} was above the highest concentration tested;
- for all three studies, the NOEC was above the water solubility of the test material;
- the results from the source of information (iii) can be used as a worst case for the Substance.

84 Based on the above, you disagree to conduct the requested study.

85 However, the reliability of this information is severely impacted by the issues described above and your comments on the draft decision do not address the identified deficiencies. Therefore, the information provided in your comments does not change the assessment, which is principally based on the reliability of the information submitted. You remain responsible for complying with this decision by the set deadline.

2.3. Study design and test specifications

86 The Substance is difficult to test due to the low water solubility (0.875 µg/L) and adsorptive properties (Log K_{ow} of 8.3). OECD TG 201 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 201. In case a dose-response relationship cannot be established (no observed effects), you must

demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

87 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).

88 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.

3. Long-term toxicity testing on aquatic invertebrates

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

3.1. Triggering of the information requirement

90 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.

91 You have provided a statement that "*High molecular weight phthlate esters have a low water solubility and experimental determination of of a measured value is technically difficult*". In Addition, in the provided a QSAR prediction (2013), the saturation concentration of the Substance in water was determined to be 0.875 µg/L.

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

3.2. Information requirement not fulfilled

93 The information provided, its assessment and the specifications of the study design are addressed under request 9.

Reasons related to the information under Annex VIII of REACH

4. In vitro micronucleus study

94 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.

4.1. Information provided

95 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 key *in vitro* chromosome aberration study in mammalian cells (2009) with the source substance diundecyl phthalate EC 222-884-9 ([redacted])
(ii) an *in vitro* chromosome aberration study in mammalian cells (1990, 1991) with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7 ([redacted])

4.2. Assessment of the information provided

4.2.1. Weight of evidence adaptation rejected

96 As explained under Section 0.2 the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

97 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII includes:

- Detection and quantification of cytotoxicity and the frequency of micronuclei in cultured mammalian cells *(in vitro*) or in mammals (*in vivo*).

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

99 The sources of information (i) and (ii) provide relevant information on detection and quantification of chromosomal aberrations in cultured mammalian cells.

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

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

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

4.2.1.1.1. The reliability provided sources of information cannot be assessed

102 To fulfil the information requirement, the study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test conducted in mammalian cells. Adequate test methods include the OECD TG 473 or the OECD TG 487 (Article 13(3) of REACH). These test methods specify that:

a) the maximum concentration tested induces 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration corresponds to 10 mM, 2 mg/mL or 2 µL/mL, whichever is the lowest;

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

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

d) the positive controls produce statistically significant increase compared with the negative control;

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

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

103 In studies (i) and (ii) described as an in vitro chromosome aberration studies in mammalian cells you did not report:

a) if the maximum tested concentration did induce 55+5% of cytotoxicity compared to the negative control, and if it did induce the precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL for studies (i) and (ii);

b) the number of metaphases scored for study (i);

c) if the positive control data induced responses compatible with those generated in the historical positive control database for studies (i) and (ii);

d) if the positive control did produce a statistically significant increase in the induced response when compared with the concurrent negative control (study ii);

e) the negative controls did not show a response within the historical control range of the laboratory for studies (i) and (ii);

f) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures were not reported for studies (i) and (ii).

104 In the absence of such information on such critical aspects of the specifications of the provided studies, ECHA cannot evaluate the reliability of the conclusions on cytotoxicity and the frequency of cells with structural chromosomal aberrations.

105 In summary, the sources of information (i) and (ii) have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause cytotoxicity and cannot provide information on the frequency of cells with structural chromosomal aberrations or the frequency of micronuclei in cultured mammalian cells.

4.2.1.2. Conclusion

106 As a conclusion, the sources of information as indicated above, provide information on in vitro chromosomal aberrations in mammalian cells. However, the reliability of these sources of information is affected by significant deficiencies.

107 Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 473 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

108 ECHA therefore considers that an appropriate in vitro micronucleus study is necessary to further investigate the mutagenicity of the Substance and to help identify the most adequate follow-up in vivo study.

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

4.3. Specification of the study design

110 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).

4.3.1. Assessment of aneugenicity potential

111 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.

112 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 fragments) and/or aneugenic events (i.e. micronuclei contain whole chromosomes).

113 [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).

5. In vitro gene mutation study in mammalian cells

114 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.

5.1. Triggering of the information requirement

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

116 The information for the in vitro gene mutation study in bacteria and for the in vitro cytogenicity study in mammalian cells or in vitro micronucleus study provided in the dossier are rejected for the reasons provided in requests 1 and 5.

117 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.

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

5.2. Information provided

119 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 key *in vitro* gene mutation study in mammalian cells (2009) with the source substance diundecyl phthalate, EC 222-884-9; diundecyl phthalate, EC 287-401-6, ([redacted]);

(ii) 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 ([redacted]).

5.3. Assessment of the information provided

5.3.1. Weight of evidence adaptation rejected

120 As explained under Section 0.2 the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

121 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII includes similar information that is produced by the OECD TG 476/490 and OECD TG 488 This includes:

- Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (*in vitro*) or mutant frequency for each tissue in mammals (*in vivo*).

122 The sources of information (i) and (ii) provide relevant information on detection and quantification of gene mutation in cultured mammalian cells. However, these sources of information have deficiencies affecting their reliability as identified and explained under Appendix on Reasons common to several requests.

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

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

5.3.1.2. Conclusion

124 As a conclusion, the sources of information as indicated above, provide information on in vitro gene mutation in mammalian cells. However, the reliability of these sources of information is affected by significant deficiencies.

125 Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 476 or an OECD TG 490 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

126 In your comments on the draft decision, you acknowledge several of the issues identified above. You disagree with ECHA's assessment and consider that an "*In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)*" is not necessary, without providing a justification. ECHA notes that your comments on the draft decision do not address the deficiencies identified above. You remain responsible for complying with this decision by the set deadline.

5.4. Specification of the study design

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

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

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

129 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 of Annex VIII or a general adaptation rule under Annex XI.

6.1. Information provided

130 You have provided the following information a short-term (7 days) study (1970) with L9-11 phthalate (No EC or CAS RN provided). In the absence of identifiers for the test material, ECHA assumes it corresponds to the Substance.

6.2. Assessment of the information provided

6.2.1. Test material not representative of the Substance

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

132 The study (i) has been conducted with UVCB substance "L9-11 phthalate". However, the robust study summary does not include information on purity, composition, degree of oligomerisation, carbon chain length, saturation, branching, and isomerisation.

133 In the absence of detailed information on the UVCB 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 Substance.

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

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

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

135 The study (i) is described as an oral 7 day toxicity study. This study has not been conducted using OECD TG 407 which investigates sub-acute toxicity. In the study:

a) the exposure duration was only 7 days;

b) the following were not described: clinical and functional observations; haematology and clinical biochemistry; as well as gross necropsy and histopathology of the organs listed in the OECD TG 407 at the end of the study.

136 The information provided does not cover the specifications required by the OECD TG 407.

137 Therefore, the information requirement is not fulfilled.

6.3. Specification of the study design

138 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.

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

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

6.4. Justification for an adaptation of the short-term repeated dose toxicity study

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

142 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.

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

144 Therefore, you are requested to either submit:

- a justification for the adaptation according to Annex VIII, Section 8.6.1., Column 2, based on request 8; or
- a 28-day study as per the study design described in 7.3 in case the 90-day study

is not requested in the adopted decision.

Reasons related to the information under Annex IX of REACH

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

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

7.1. Information provided

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

(i) a sub-chronic repeated dose toxicity study type (1993) with the source substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters, EC 275-809-7 (L8-10P-Sasol)

7.2. Assessment of the information provided

7.2.1. Read-across adaptation rejected

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

7.2.1.1. Source study not adequate for the information requirement

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

a) clinical signs are observed daily, and functional observations (i.e. sensory activity, grip strength and motor activity assessments) are made during week 11 or later;
b) the oestrus cycle in females is examined at necropsy;
c) terminal organ and body weights are measured;
d) full histopathology is performed as specified in the test guideline.

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

a) The following clinical signs and functional aspects were not assessed: nature, severity and duration; In particular, the following investigations are missing: neurobehavioural examination, circulating thyroid hormones (T4, T3, TSH);
b) oestrus cyclicity was not assessed;
c) terminal organ weights and organ/body weight ratios were not recorded;
d) the following histopathology items were not studied: incidence and severity. In particular, the following investigations are missing: adrenals, pituitary, small and large intestines, gall bladder, skeletal muscle, bone, and bone marrow.

150 The information provided does not cover the specifications required by the OECD TG 408.

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

152 In your comments on the draft decision, you acknowledge the issues identified above. You state your intent to "*re-evaluate the existing read-across approach*". As already addressed under '0.1.3 Conclusion on the read-across approach', you propose a strategy to improve your adaptation under Annex XI, Section 1.5. (grouping of substances and read-across approach). However, as this strategy relies essentially on data, which is yet to be generated, no assessment can currently be made by ECHA. You remain responsible for complying with this decision by the set deadline.

7.3. Specification of the study design

153 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.

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

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

8. Long-term toxicity testing on aquatic invertebrates

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

8.1. Information provided

157 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 1,2-Benzenedicarboxylic acid, di-C9-11-alkyl esters, EC 272-012-6 ([redacted])

(ii) a long-term toxicity study on *daphnia magna* (1998), performed according to OECD TG 202 (1984) with the category member Diundecyl phthalate, branched and linear, EC 287-401-6 ([redacted])

(iii) a long-term toxicity study on *daphnia magna, non guideline* (1997) with the category member Diundecyl phthalate, branched and linear, EC 287-401-6

8.2. Assessment of the information provided

8.2.1. Weight of evidence adaptation rejected

158 As explained under Section 0.2 the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

159 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.

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

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

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

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

163 As explained in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. Thus, you have not established that the information on the analogue substances used in the sources of information (i)-(iii) can reliably contribute to your weight of evidence adaptation.

164 In addition, the reliability of the source of information (i), (ii) and (iii) is also affected by the following issue:

8.2.1.1.1. The reliability provided sources of information cannot be assessed

165 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). The substances referred to in studies (i) to (iii) are difficult to test due to their low water solubility (for instance, in the all of the source of information (i) - (iii), the (mean) measured concentrations were <1 mg/L). The specifications of OECD TG 211 and OECD GD 23 include:

166 *Reporting of the methodology and results*

a) the test design is reported (semi-static or flow-through, number of replicates, number of parents per replicate).
b) 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.
c) the full record of the daily production of living offspring during the test by each parent animal is provided.
d) the number of deaths among the parent animals (if any) and the day on which they occurred is reported.

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

f) As explained above, the tested analogue substances are difficult to test. Therefore the following additional information must be provided:

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

167 *Reporting of the methodology and results*

b) TOC and temperature range are not reported in the source information (i) and none of the parameters were reported in the source of information (ii).

c) - d) are not reported in both sources of information (i) and (ii).

e) adequate information on the analytical method (including performance parameters of the method) is reported in the neither sources of information (i) nor in (ii).

168 For the source of information (iii);

169 *Reporting of the methodology and results*

a) -f) you have not provided any of the information listed above.

170 Based on the above, the reporting of the studies is not sufficient to conduct an independent assessment of their reliability. More specifically, key elements of the study design (source of information (iii)) 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.

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

8.2.1.2. Conclusion

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

173 Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 211 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

174 In your comment to the draft decision, you acknowledge the deficiencies in the provided sources of information (i)-(iii). However, you explain why you believe that the sources of the information (i)-(iii) should still be considered as valid source of information under a weight of evidence approach as:

- the studies in the sources of information had been performed in 1990s, whereas the OECD TG 211 was updated in 2012;

- although now raw data is available, the sources of information (i)-(iii) are from peer reviewed journal with a good reputation (namely, Chemosphere and Environmental Toxicology and Chemistry);
- for all three studies, the NOEC was above the water solubility of the test material;
- the source of the information (i), which was performed with the Substance, showed no effect and was used as (no) effect concentration for risk assessment.

175 Based on the above, you disagree to conduct the requested study.

176 However, the reliability of this information is severely impacted by the issues described above and your comments on the draft decision do not address the identified deficiencies. Concerning your statement that study (i) was conducted with the Substance, ECHA notes that you have provided no supporting information to demonstrate that the test material used in this study corresponds to the Substance. Therefore, the information provided in your comments does not change the assessment, which is principally based on the reliability of the information submitted. You remain responsible for complying with this decision by the set deadline.

8.3. Study design and test specifications

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

Reasons related to the information under Annex X of REACH

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

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

9.1. Information provided

179 You have not provided any information for this information requirement.

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

181 In your comments on the draft decision, you do not agree to perform the requested study. To support your position, you provide the following statement: "*no gain in information is expected when testing the second species*" and refer to two studies ([redacted], 2019 and [redacted], 2008) which, according to you, demonstrate respectively that rat and rabbit "*do not differ in sensitivity to developmental effects*" and "*in general were comparably sensitive towards chemicals with respect to developmental toxicity*". In the comments to the draft decision, you state further that: "*pre-natal developmental toxicity study in a second species will result in unnecessary death of animals, being against the best interest of animal welfare and therefore the Registrant asks that this request will not be included in the final decision*".

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

9.2. Specification of the study design

183 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species. The study in the first species was carried out by using a rodent species (rat).

184 Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

185 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).

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

References

The following documents may have been cited in the decision.

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

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

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

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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

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

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

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 07 December 2021.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. The standard deadline granted by ECHA has been exceptionally extended by 12 months to take into account currently longer lead times in contract research organisations. ECHA has also notified draft decisions to the registrant of other substances belonging to the category you have formed.

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

ECHA took into account your comments and removed the request for ready biodegradability (Annex VII, Section 9.2.1.1.).

In your comments to the draft decision you request an extension of the deadline from 36 to 44 months based on the following reasons:

- Limited CRO capacity as supported by a CRO letter. The schedule provided by the CRO indicates that the OECD TG 414 in a second species would be completed within 39 months.
- You also consider that 5 extra months are need for "*IUCLID update + revision of read-across justification*", following the completion of the OECD TG 414 study in a second species.

ECHA acknowledges the additional time needed to complete testing due to anticipated delays posed by an appropriate laboratory. The evidence you provided supports extending the deadline to 39 months, which includes completion of the PNDT study in a second species. The timeline set in this decision allows for generating the standard information requirements covered by this decision. In case you decide to submit an adaptation instead of the requested study(ies), it remains your responsibility to provide a compliant adaptation by the set deadline.

On this basis, and based on the documentary evidence provided, ECHA has agreed with your request for a deadline extension and has extended the deadline to 39 months.

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

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

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

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

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

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

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

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

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

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:

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

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

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as

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

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

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.

[3] https://echa.europa.eu/manuals