~~Confidential~~

Helsinki, 11 October 2023

Addressee
Registrant of JS for DIUP / EM as LR (multi) as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
10/07/2015

Registered substance subject to this decision ("the Substance")
Substance name: 1,2-benzenedicarboxylic acid, di-c10-12-branched alkyl esters
EC number/List number: 700-989-5

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***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. Skin sensitisation (Annex VII, Section 8.3.)
   a) *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and
   b) only if the *in vitro/in chemico* test methods specified under point a) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429)

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

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

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

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

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

6. 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)

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

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

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

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

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

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

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

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

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

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. 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:

- Skin sensitisation (Annex VII, Section 8.3.)
- 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.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Long-term toxicity testing on 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 your CSR.

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

- DTDP 1,2- Benzenedicarboxylic acid, di-C11-14- branched alkyl esters, C13-rich EC 271-089-3, CAS RN 68515-47-9 (source substance 1);
- L9-11P 1,2-Benzenedicarboxylic acid di-C9-11-branched and linear alkyl esters, EC 271-085-1, CAS RN 68515-43-5 (source substance 2);
- DIDP 1,2-Benzenedicarboxylic acid di-C9-11-branched alkyl esters, C10-rich, EC 271-091-4, CAS RN 68515-49-1 (source substance 3);
- DINP 1,2-Benzenedicarboxylic acid di-C8-10-branched alkyl esters,C9-rich, EC 271-090-9, CAS NR 68515-48-0 (source substance 4);
- DIUP, 1,2-benzenedicarboxylic acid, di-C10-12-branched alkyl esters, C11-rich, EC 287-401-6, CAS RN 85507-79-5 (source substance 5). ECHA assumes EC 287-401-6 corresponds to EC 700-989-5;
- DIDP, 1,2-benzenedicarboxylic acid, di-isodecyl ester, EC 247-977-1, CAS RN 26761-40-0 (source substance 6);
- DUDP, diundecyl phthalate, EC 222-884-9, CAS RN 3648-20-2 (source substance 7) ;
- D79P, 1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, EC 271-083-0, CAS RN 68515-41-3 (source substance 8);
- DnOP, dioctyl phthalate, EC 204-214-7, CAS RN 117-84-0 (source substance 9).

7 You justify the grouping of the substances as: "*the target and source substance belong to the High Molecular Weight Phthalate Ester (HMWPE) Category which was established based on structural similarity.* […] *these substances are similar in molecular structure, physicochemical properties, use, and manufacturing processes. Based on these unifying considerations, the variation in carbon backbone length among these analogues is not expected to significantly impact toxicity. When possible data from the source substance(s) with a carbon backbone length closest to target substance was preferred and used to 6uehle individual endpoints. Therefore, it is scientifically reasonable to predict the toxicological properties for the registered substance from the properties determined for the analogues*".

8 In the comments to the draft decision, you suggest a different read-across approach for human health endpoints based on a category of three high molecular phthalates (DIDP with EC 271-091-4, DIUP with EC 700-989-5 and DTDP with EC 271-089-3). We understand from your comments that you propose a "*phase approach to testing*" to decide between performing the studies (skin sensitisation, mutagenicity, reproductive and developmental endpoints) with the Substance or relying on using grouping and read-across approaches.

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

0.1.1.1. Incomplete description of the applicability domain of the category

10 A category (grouping) hypothesis should address "*the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint*" (Guidance on IRs and CSA, Section R.6.2.4.1.). Particularly, the applicability domain identifies "the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made" (Guidance on IRs and CSA, Section R.6.2.1.2.). Therefore, to reliably predict properties within a category, the applicability domain should be described. Such description must cover the borders of the category, define unambiguous inclusion- and exclusion criteria, and must include a justification for these.

11 You describe the members of the category as substances belonging to the High Molecular Weight Phthalate Ester (HMWPE). However, you do not specify any applicability domain.

12 This applicability domain does not introduce unambiguous inclusion/exclusion criteria which would identify the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made for the (sub)category members.

0.1.1.2. Incomplete characterisation of the Substance and source substances

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

14 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.).

15 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.

16 In your read-across justification document, you provide the following information on the target and source substances:

- Target: you specify that the Substance has a low probability of having highly branched isomers or significant ethyl branching. In addition, you state that the backbone chain length of the Substance is expected to contain at least 7 carbon atoms, with the majority being 9 carbon atom or higher.
- DTDP/Source substance 1: you specify that DTDP is generated from a C13 alcohol with some C12 and C14 isomers. In addition, you state that DTDP (CAS 2725-26-5) is more linear but related to DTDP (the source substance 1) and expected to have a similar level and type of branching as the Substance. In 'Figure1: Percent Primary Alcohol Backbone Length', you indicate that the Substance contains C9-C12 backbones.
- L9-11P/Source substance 2: you specify that D911P is generated from "[redacted], in which the alkyl moieties have a carbon distribution of [redacted]% in the range C9 to C11, with following typical C-chain length distribution: C9: [redacted] %; C10: [redacted]% and C11: [redacted]%). In addition, you state that D911P is highly linear (minimum 80%) with predominantly mono-2-methyl branching in the reminder and is expected to have less branches than the Substance. In 'Figure1: Percent Primary Alcohol Backbone Length', you indicate that the Substance contains C9-C11 backbones.
- DIDP/Source substance 3: you specify that DIDP is generated from a C10 [redacted] which is C10 rich and some C8, C9 and C11 isomers. In addition, you state that DIDP is expected to have a similar level and type of branching as the Substance with alkyls of a shorter chain length than the Substance. In ' Figure1: Percent Primary Alcohol Backbone Length', you indicate that DIDP contains C7-C9 backbones.
- DINP/Source substance 4: you specify that DINP is generated from an [redacted] and contains mainly C9- branched isomers and C9-10 branched isomers. In 'Figure1: Percent Primary Alcohol Backbone Length', you indicate that DINP contains C6-C8 backbones.
- DIUP/Source substance 5: In 'Figure 1: Percent Primary Alcohol Backbone Length' and 'Figure 2: Developmental and Reproductive Summary Figure', you indicate that DIUP contains C8-C10 backbones.
- DIDP/Source substance 6: In 'Figure 2: Developmental and Reproductive Summary Figure', you indicate that DIDP contains C7-C9 backbones.
- DUDP/Source substance 7: You state that "… *(DUDP; CAS 3648-20-2)… is described as having over* [redacted]*% a straight ester side chain of eleven carbons, and with some methyl C10 branched material (total carbon number (C11), mainly C11 with some C10 backbone). DUDP shares the same number of carbons in the alkyl chain as the registered substance with overlap of the longest linear carbon chain lengths. This substance overlaps the registered substance and brackets the high end of the alkyl chain analogue read across*". In 'Figure 1: Percent Primary Alcohol Backbone Length' and 'Figure 2: Developmental and Reproductive Summary Figure', you indicate that DUDP contains C10-C11 backbones.
- D79P/Source substance 8: You state that the substance is "*at least* [redacted]*% linear, with predominantly* [redacted]". In 'Figure 1: Percent Primary Alcohol Backbone Length', you indicate that D79P contains C7-C9 backbones.

- DnOP/Source substance 9: In 'Figure 1: Percent Primary Alcohol Backbone Length', you indicate that DnOP contains C8 backbones.

17 However, the target and source substances 1 to 9 listed above, you fail to provide a comprehensive description of the distribution of alkyl chain length and the branching of alkyl side carbon chain (i.e., isomeric composition) for the target and source substances supported by adequate scientific evidence.

18 In your comments to the draft decision you claim that the composition of the registered substance is fully described in an attachment to your IUCLID dossier. ECHA acknowledges that IUCLID Section 1.4. includes a document entitled '[redacted]'. In this document, you provide an estimate of the relative amount of C10, C11 and C12 isomers and of their branching index by GC analysis. You state that the Substance includes "*over two hundred isomers*" and that you could not determine their specific structure based on the analytical techniques available to you. You report that the main fractions of the Substance include Di-Branched C10 ([redacted] %) and Tri-Branched C10 ([redacted]%). Finally you claim that, to obtain adequate plasticizer performance in flexible PVC, "*it is absolutely critical to control the degree of branching of plasticizers and avoid highly branched plasticizers*".

19 ECHA maintains that the document referred to in your comments does not provide adequate information to precisely characterize the branching of alkyl side carbon chain (i.e., isomeric composition) as acknowledged by you in that document. In particular, while you claim that the Substance is expected to contain at least 7 carbon atoms (with the majority being 9 carbon atom or higher), the document does not provide evidence that no Di- and Tri-Branched C10 constituents would have a backbone of less than 7 carbon atoms.

20 In addition, the studies addressed in requests 1, 2, 5, 6, 7, 8, 9 and 10 have been conducted with the source substances 2, 3, 4, 5, and/or 6, contain only limited further information besides CAS and EC numbers.

21 More specifically, you have only provided the purity for:

- Request 1: EC 287-401-6 in a Buehler study (1994): [redacted]% analytical purity
- Request 7: EC 247-977-1 in a 28-day repeated dose toxicity study (1990): "*ester content:* [redacted]*% w/w*"
- Request 9: EC 271-083-0 (purity [redacted]% (m/m)) and EC 271-085-1 (purity [redacted]% (m/m)) in pre-natal developmental toxicity study in rodents (rats) (2001) and EC 222-884-9 (>[redacted]% pure) in a pre-natal developmental toxicity study in rodents (rats) (2013).
- Request 10: EC 287-401-6 and EC 222-884-9 (>purity [redacted] %) in long-term aquatic invertebrate studies.

22 For the substances tested in the studies addressed in requests 1, 2, 5, 6, 7, 8, 9 and 10, no information has been provided on (purity), composition, carbon chain length, branching, isomerisation.

23 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.

24 Despite of the above issues, ECHA understands that you rely on the category of "*high molecular weight phthalates (HMWPE)*" in order to meet the information requirements for the Substance, and your predictions are assessed on this basis.

0.1.1. Predictions for (eco)toxicological properties

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

0.1.1.1. Insufficient data density

26 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".

27 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.

28 You have provided

- Growth inhibition study aquatic plants study with one category member (EC 222-884-9)
- Long-term aquatic invertebrate studies on two category members (EC 222-884-9 and 287-401-6).
- Two skin sensitization studies with category member EC 287-401-6
- One in vitro gene mutation study in bacteria with category member EC 247-977-1.
- One in vivo mammalian erythrocyte micronucleus test with category member EC 271-091-4
- One in vitro gene mutation study in mammalian cells with category member EC 247-977-1
- Sub-acute repeated dose toxicity studies with category members EC 247-977-1 (two studies) and EC 271-090-9 (one study)
- Sub-chronic toxicity studies with category members EC 271-091-4 (one study) and EC 247-977-1 (one study)
- Pre-natal developmental toxicity studies with EC 247-977-1 (one study), EC 271-091-4 (two studies), EC 222-884-9 (one study), EC 271-083-0 (one study), EC 271-085-1 (one study), EC 204-214-7 (one study).

29 The proposed category of "*high molecular weight phthalates*" includes substances with side chains ranging from C6 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.

0.1.1.2. Missing supporting information to compare properties of the substances

30 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.).

31 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substance(s) cause the same type of effect(s). In this context, relevant,

reliable and adequate information allowing to compare the properties of the substance(s) is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

32 A data matrix is provided comparing the results of mammalian toxicology studies between the Substance and the analogue substances EC 271-091-4, EC 271-090-9, and EC 271-085-1. According to this table the only endpoint with data on source substances EC 271-091-4 and EC 271-090-9 and the Substance is skin sensitization. However, no robust study summaries (RSS) of these studies are provided. In addition, skin sensitization cannot be used as bridging data to compare systemic toxicology properties of the Substance.

33 In the new read-across approach provided in your comments to the draft decision, you invoke a "*phased bookend testing strategy*" for human health relying on the generation of additional supporting information on the Substance and on the analogue substances. You intend to conduct OECD 408-Sub-chronic 90-day studies on three substances (DIDP, DIUP and DTDP) "*to act as bridging studies to inform read-across hypothesis for skin sensitization, mutagenicity, reproductive and developmental endpoints*".

34 Your strategy relies essentially on data, which is yet to be generated, therefore no conclusion on the adequacy of the bridging information you intend to generate can currently be made.

35 Overall, 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 carbon chain length as well as the branching of the alkyl chain would not impact the prediction.

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

0.1.1.3. Inadequate or unreliable studies on the source substances

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

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

38 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the requests 2, 4, 7, 8, 9 and 10. Therefore, no reliable predictions can be made for these information requirements.

0.1.1. Conclusion on the read-across approach

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

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

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

1.1. Information provided

41 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 buehler study (1994), with the source substance 1,2-benzenedicarboxylic acid, di-C10-12-branched alkyl esters, C11-rich, EC 287-401-6, CAS RN 85507-79-5;

(ii) a HRIPT study (1995/1999), with the source substance 1,2-benzenedicarboxylic acid, di-C10-12-branched alkyl esters, C11-rich, EC 287-401-6, CAS RN 85507-79-5.

1.2. Assessment of the information provided in your dossier

1.2.1. Assessment whether the Substance causes skin sensitisation

1.2.1.1. Read-across adaptation rejected

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

1.2.2. No assessment of potency

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

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

45 Therefore, the information requirement is not fulfilled.

46 In the comments to the draft decision, you make a statement that "*there is an in vivo study conducted in guinea pig on the Registered Substance (DIUP) in 1994*". However, as the information is currently not available in your comments nor your registration dossier, the data gap remains. Therefore, no conclusion on compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

1.3. Specification of the study design

47 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided.

Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

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

2. *In vitro* gene mutation study in bacteria

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

2.1. Information provided

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

(i) an *in vitro* gene mutation study in bacteria (1985), with the source substance Di-isodecyl Phthalate, EC 247-977-1.

2.2. Assessment of the information provided

2.2.1. Read-across adaptation rejected

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

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

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

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

53 In study(i):

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

54 Therefore, the studies 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.

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

56 Therefore, the information requirement is not fulfilled.

57 In the comments to the draft decision, you agree with ECHA's assessment. You "*plan to decide how to address this endpoint (read across vs experimental study) in a phased approach to testing*".

58 ECHA takes note of your intentions. You remain responsible for complying with this decision by the set deadline.

2.3. Specification of the study design

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

3. Long-term toxicity testing on aquatic invertebrates

60 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

61 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.

62 You have provided information which indicates that the Substance includes constituents that are poorly water soluble. The reported water solubility of the Substance is 0.00000441 mg/L at 25°C based on a publication (2007) and calculation (2000) based on quantitative structure-property relationship) three-solubility model.

63 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

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

3.3. Study design and test specifications

65 The Substance is difficult to test due to the low water solubility (0.00441 µg/L) and adsorptive properties (Log K_{ow} >10) and surface activity (Surface tension 30.9 mN/m). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 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.

66 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).

67 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. Growth inhibition study aquatic plants

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

4.1. Information provided

69 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) Growth inhibition study on aquatic algae, performed according to the USEPA 600/9-78-018, Printz Algal Assay (1997), with the source substance Di-n-undecyl Phthalate, EC 222-884-9.

4.2. Assessment of the information provided in the dossier

4.2.1. Read-across adaptation rejected

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

4.2.1.1. Inadequate or unreliable study (i) on the source substance

71 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed 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 requirements of OECD GD 23 if the substance is difficult. The

substances referred to in studies (i) is difficult to test due to its low water solubility. Therefore, the following specifications must be met:

Reporting of the methodology and results

a) the test design is reported (*e.g.*, number of replicates);

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

c) the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported.

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

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

f) as explained above the Substance is 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.

72 In study (i):

Reporting of the methodology and results

a) you did not report the number of replicates. In your comment to the draft decision, you provide the information on the replicates;

b) You do not report the test medium composition. In addition, biomass density at the beginning of the test;

c) You do neither specify the method used to determine the algal cell density nor provide evidence of correlation between the measured parameter and dry weight. In your comment to the draft decision, you provide information that biomass was determined based on chlorophyll a concentrations.

d) You do not provide the results in tabular form, containing the required information. You state that "*Control chlorophyll or cell counts were not reported*" In your comment to draft decision, you acknowledge that this information is not included in the study report;

e) You indicate that analytical monitoring was performed but you neither specify the method used nor provide performance parameters of the method. You provide the initial measured concentration (3.3 mg/L) and mean of the measured concentrations at the start and end of the study (2.1 mg/L) only. In your comments to the draft decision, you provide following statement: "*analytical results would indicate emulsification may have occurred such that concentrations in excess of saturation were indicated at the beginning and end of exposure (3.3 and 0.9 mg/L, respectively). It is apparent that no physical effects unrelated to chemical toxicity occurred, and no effects related to chemical toxicity occurred; and there were no significant inhibitory effect (max 4% inhibition in chlorophyll a at 72h) during the study; and the results can be reported as "no toxic effects at saturation".*

f) You did not provide the information listed above. In your comments to the draft decision, you state that sonication was used to prepare the test solution but you did not provide the other information listed above.

73 Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, as you have not provided the information listed under point b), d), e) and f), ECHA is not in a position to assess whether the validity criteria of the test guideline were met, whether the test conducted under conditions that are consistent with the requirements of the OECD TG 201 and OECD GD 23, and to assess the interpretation of the study results.

74 Therefore, the study (i) does not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 201 and therefore, the study (i) is not an adequate basis for your read-across predictions.

75 Therefore, the information requirement is not fulfilled.

76 In the comments to the draft decision, you provide some additional information on the study but you agree with the shortcomings in the reporting of that study. You state that you "*propose to add a QSAR prediction as the key study (endpoint study record: Toxicity to aquatic algae and cyanobacteria/DIUP/700-989-5/Q), using the ester model from ECOSAR v2.0.*" However, the corresponding QSAR prediction is not provided in your comments. Therefore, no assessment can be conducted. You remain responsible for complying with this decision by the set deadline.

4.3. Study design and test specifications

77 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.

Reasons related to the information under Annex VIII of REACH

5. *In vitro* micronucleus study

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

5.1. Information provided

79 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 vivo* mammalian erythrocyte micronucleus test (2000), with the source substance 1,2-Benzenedicarboxylic acid di-C9-11-branched alkyl esters, C10-rich, EC 271-091-4, CAS RN 68515-49-1.

5.2. Assessment of the information provided

5.2.1. Read-across adaptation rejected

80 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.

81 Therefore, the information requirement is not fulfilled.

82 In the comments to the draft decision, you agree with ECHA's assessment. You "*plan to decide how to address this endpoint (read across vs experimental study) in a phased approach to testing*".

83 ECHA takes note of your intentions. You remain responsible for complying with this decision by the set deadline.

5.3. Specification of the study design

84 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).

5.3.1. Assessment of aneugenicity potential

85 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.

86 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)).

[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).

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

87 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.

6.1. Triggering of the information requirement

88 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.

89 The information for the in vitro gene mutation study in bacteria and for the in vitro micronucleus study provided in the dossier are rejected for the reasons provided in requests 2 and 5.

90 The result of the requests for an in vitro gene mutation study in bacteria and for an in vitro micronucleus study 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.

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

6.2. Information provided

92 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 (1986), with the source substance 1,2-benzenedicarboxylic acid, di-isodecyl ester, EC 247-977-1, CAS RN 26761-40-0.

6.3. Assessment of the information provided

6.3.1. Read-across adaptation rejected

93 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.

94 Therefore, the information requirement is not fulfilled.

95 In the comments to the draft decision, you agree with ECHA's assessment. You "*plan to decide how to address this endpoint (read across vs experimental study) in a phased approach to testing*".

96 ECHA takes note of your intentions. You remain responsible for complying with this decision by the set deadline.

6.4. Specification of the study design

97 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.

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

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

7.1. Information provided

99 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 21-day repeated dose toxicity study (1986), with the source substance 1,2-benzenedicarboxylic acid, di-isodecyl ester, EC 247-977-1, CAS RN 26761-40-0;

(ii) a 28-day repeated dose toxicity study (1990), with the source substance 1,2-benzenedicarboxylic acid, di-isodecyl ester, EC 247-977-1, CAS RN 26761-40-0;

(iii) a short-term repeated dose toxicity study (1969), with the source substance 1,2-Benzenedicarboxylic acid di-C8-10-branched alkyl esters,C9-rich, EC 271-090-9, CAS NR 68515-48-0.

(iv) a two-week inhalation study (1981), with the source substance 1,2-Benzenedicarboxylic acid di-C9-11-branched alkyl esters, C10-rich, EC 271-091-4, CAS RN 68515-49-1.

7.2. Assessment of the information provided

7.2.1. Read-across adaptation rejected

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

7.2.1.1. Inadequate or unreliable studies (i) to (iii) on the source substances

101 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed and 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;

In study (iii) only one dose level was described.

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

In study (ii) only males were included in each test and control group.

In study (iii) only 4 males and 4 females were included in each test and control group.

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

In study (i) the exposure duration was only 21 days.

d) haematological and clinical biochemistry tests are performed as specified in paragraphs 32-39 of the test guideline;

In studies (i and ii) the following haematology investigations were missing: haematocrit, haemoglobin concentrations, erythrocyte count, reticulocytes, total and differential leucocyte count, platelet count and a measure of blood clotting time/potential.

In study (i) the following clinical biochemistry investigations were missing: sodium, potassium, glucose, urea, creatinine, total protein and albumin, and bile acids

In study (i) the following clinical biochemistry investigations were missing: sodium, potassium, glucose, total cholesterol, urea, creatinine, total protein and albumin, and bile acids.

e) full histopathology, including incidence and severity, is performed as specified in paragraphs 47-49 of the test guideline;

In studies (i and ii) the following histopathology items were not reported: ovaries, epididymides, prostate and seminal vesicle, uterus, adrenal, thyroid, vagina.

In study (iii) the following histopathology items were not studied: spleen, adrenals, heart (as specified in the OECD TG 407 available at the time of the study).

102 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameter(s) of the corresponding OECD TG (studies (i, ii, and iii)), and do not cover an exposure duration comparable to or longer than the one specified in the corresponding OECD TG (study (i)).

7.2.1.2. Inadequate or unreliable inhalation study on the source substance (study iv)

103 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed and 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 412. 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) at least 5 male and 5 female animals are used for each concentration and control group;

c) the test material is dosed for a minimum of 6h/day, on a 5 day per week basis for a period at least 28 day;

d) food consumption is measured at least weekly;

e) body weights are measured at least twice per week;

f) clinical observations are made before, during, and after each exposure period as well as during the post-exposure periods;

g) haematological and clinical biochemistry tests are performed as specified in paragraphs 48-49 of the test guideline;

h) terminal organ and body weights are measured;

i) gross pathological examinations are performed as specified in paragraphs 53-56 of the test guideline;

j) full histopathology is performed as specified in paragraph 57 of the test guideline;

k) bronchoalveolar lavage (BAL) is performed as specified in paragraph 50 of the test guideline (also in satellite groups if applicable);

104 In study (iv):

a) there was only one dose level;

b) 8 males and no females were used in each concentration and control group;

c) the exposure duration was only 14 days (10 total exposures);

d) food consumption was not assessed;

e) body weights and body weight changes were not assessed;

f) haematology and clinical biochemistry were not performed;

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

h) gross pathology was not assessed;

i) histopathology was not assessed;

j) BAL analysis was not performed.

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

7.2.1.3. Study not conducted by the most appropriate route (studies iii and iv)

106 According to the 'Guidance on IRs and CSA, Section R.7.5.4.3.2.', the default route is oral. However, the dermal or the inhalation route may be more appropriate, depending on the physico-chemical properties of the Substance, the most relevant route of human exposure, and other toxicological considerations.

107 Under Annex VIII, Section 8.6.1., Column 2, Paragraph 2, the appropriate route shall be chosen on the following basis:

108 Testing by the dermal route is appropriate if:

- inhalation of the substance is unlikely, and
- skin contact in production and/or use is likely, and
- the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin.

109 Testing by the inhalation route is appropriate if:

- exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.

110 The study (iii) was performed with exposure via the dermal route. According to IUCLID section 7.1., dermal absorption of the Substance is low. You did not provide a justification for the choice of the dermal route of exposure. You have not demonstrated that the dermal route is the most appropriate route of exposure.

111 The study (iv) was performed with exposure via the inhalation route. Regarding the Substance, you state that the vapour pressure is low and reported no uses where inhalation is expected. You have not demonstrated that the inhalation route is the most appropriate route of exposure.

112 The oral route is the most appropriate route, as none of the criteria listed above for the dermal route or the inhalation route are met.

113 Based on the above, the provided studies (iii and iv) are not performed according to the appropriate route .

114 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance.

115 Therefore, the information requirement is not fulfilled.

7.3. Specification of the study design

116 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, for the reasons specified under 7.2.1.3.

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

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

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

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

120 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.

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

122 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.

123 In the comments to the draft decision, you indicate that "an adaptation for the short-term repeated dose toxicity has been added to the registered substance dossier and provided in attachment". However, the information is currently still not available in your registration dossier. Therefore, the data gap remains. You must submit this information in an updated registration dossier by the deadline set in the decision.

Reasons related to the information under Annex IX of REACH

8. Sub-chronic toxicity study (90 days)

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

8.1. Information provided

125 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-chronic study (1968), with the source substance 1,2-benzenedicarboxylic acid, di-isodecyl ester, EC 247-977-1, CAS RN 26761-40-0.

8.2. Assessment of the information provided

8.2.1. Read-across adaptation rejected

126 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 issues addressed below.

8.2.1.1. Inadequate or unreliable study (i) on the source substance

127 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:

a) the oestrus cycle in females is examined at necropsy.

128 In study (i):

a) oestrus cyclicity was not assessed;

129 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 parameter of the corresponding OECD TG.

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

131 Therefore, the information requirement is not fulfilled.

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

8.3. Specification of the study design

133 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.

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

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

9. Pre-natal developmental toxicity study in one species

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

9.1. Information provided

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

(i) a pre-natal developmental toxicity study in rodents (mice) (1987), with the source substance 1,2-benzenedicarboxylic acid, di-isodecyl ester, EC 247-977-1, CAS RN 26761-40-0;

(ii) a pre-natal developmental toxicity study in rodents (rats) (1995 and 1999), with the source substance 1,2-Benzenedicarboxylic acid di-C9-11-branched alkyl esters, C10-rich, EC 271-091-4, CAS RN 68515-49-1;

(iii) a pre-natal developmental toxicity study in rodents (rats) (1997), with the source substance 1,2-Benzenedicarboxylic acid di-C9-11-branched alkyl esters, C10-rich, EC 271-091-4, CAS RN 68515-49-1;

(iv) a pre-natal developmental toxicity study in rodents (rats) (2013), with the source substance diundecyl phthalate, EC 222-884-9, CAS RN 3648-20-2;

(v) a pre-natal developmental toxicity study in rodents (rats) (2001), with the source substance 1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, EC 271-083-0, CAS RN 68515-41-3 and 1,2-Benzenedicarboxylic acid di-C9-11-branched and linear alkyl esters, EC 271-085-1, CAS RN 68515-43-5;

(vi) a pre-natal developmental toxicity study in rodents (rats) (2011), with the source substance dioctyl phthalate, EC 204-214-7, CAS RN 117-84-0;

9.2. Assessment of the information provided

9.2.1. Weight of evidence adaptation rejected

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

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

140 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they

together provide sufficient weight to conclude on the corresponding information requirement.

9.2.1.1. Lack of documentation justifying the weight of evidence adaptation

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

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

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

144 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.

9.2.1.2. Pre-natal developmental toxicity

145 Pre-natal developmental toxicity includes information after pre-natal exposure on embryonic/foetal survival (number of live foetuses; number of resorptions and dead foetuses, post implantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

146 Studies (ii, iv, v and vi) may provide relevant information on pre-natal development. The RSS you have provided for study (i) does not specify if and to what extent pre-natal development was studied. Study (iii) may provide limited relevant information on pre-natal development, but does not inform on external, visceral, or skeletal alterations.

9.2.1.3. Maternal toxicity

147 Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

148 Studies (ii, iii, iv, v and vi) may provide relevant information on maternal toxicity. The RSS you have provided for study (i) does not specify if and to what extent maternal toxicity was studied.

9.2.1.4. Maintenance of pregnancy

149 Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

150 Studies (ii, iv, v and vi) may provide relevant information on the maintenance of pregnancy. The RSS you have provided for study (i) does not specify if and to what extent the maintenance of pregnancy was studied. Study (iii) may provide limited relevant information on the maintenance of pregnancy, but does not inform on the number of animals aborting or delivering early, or the number and percent of pre- and post-implantation losses.

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

9.2.1.5. Read-across adaptation rejected

152 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.

9.2.1.5.1. The provided studies (i) and (vi) do not meet the specifications of the test guidelines

153 The property investigated shall normally result from a study performed in accordance with OECD TG 407. This guidance includes the following specifications:

a) at least three dose levels are tested (unless conducted at the limit dose) with concurrent controls;

b) at least 20 female animals with implantation sites for each test and control group are included;

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

d) the study is conducted in rats or rabbits.

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

a) only one dose level was included in study (i);

b) the number of females used in each test and control group is not specified in study (vi);

c) the exposure duration was limited to GD6-GD13 in study (i);

d) the study was conducted in mice without justification in study (i).

155 In summary, the source of information (i) has critical reliability issues with regard to an insufficient number of doses used, insufficient exposure duration, and the unjustified use of a non-rat species. These issues make the presented results unreliable, because it is impossible to make considerations related to dose-response, not all potential adverse outcomes are covered due to the limited exposure duration, and species-specific effects may affect the study outcome, respectively. With regards to study (vi), not having any data on the number of animals used is a critical reliability issue, as this information is required to assess the statistical power of the study.

156 In the absence of such information on critical aspects of the specifications of the provided studies, ECHA cannot evaluate the reliability of the conclusions on the pre-natal developmental toxicity.

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

9.2.1.6. Conclusion

158 As a conclusion, the sources of information as indicated above, provide relevant information on Pre-natal developmental toxicity study. However, the reliability of this information is severely impacted by the issues listed above.

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

160 In the comments to the draft decision, you agree with ECHA's assessment. You "*plan to decide how to address this endpoint (read across vs experimental study) in a phased approach to testing*".

161 ECHA takes note of your intentions. You remain responsible for complying with this decision by the set deadline.

9.3. Specification of the study design

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

163 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).

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

10. Long-term toxicity testing on aquatic invertebrates

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

10.1. Information provided

166 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 long-term toxicity study on *Daphnia magna* (1998), performed according to the OECD TG 211, with the source substance 1,2-benzenedicarboxylic acid, di-C10-12-branched alkyl esters, C11-rich, EC 287-401-6/ CAS NR 85507-79-5// DIUP;

(ii) a long-term toxicity study on *Daphnia magna* (1995) performed according to the US EPA 560/6-82-002, with the source substance, EC 222-884-9/ CAS RN 3648-20-2 // DUP.

167 In the comments to the draft decision, you have submitted:

(iii) a QSAR prediction in accordance with Annex XI, Section 1.3, using the ester model from ECOSAR v.2.0.

10.2. Assessment of the information provided in your dossier

10.2.1. Read-across adaptation rejected

168 While you have not claimed that the information obtained in the study (i) conducted with the source substance (EC 287-401-6) is obtained from another substance than the Substance, the information on the test material identity (i.e. EC and CAS numbers) provided in your dossier currently corresponds to another registered substance. Therefore, ECHA understands that the study (i) was conducted with analogue substance and evaluated it as a read-across adaptation under Annex XI, Section 1.5 of REACH.

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

10.2.1.1. Inadequate or unreliable studies on the source substance(s)

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

Reporting of the methodology and results

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

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

c) water quality monitoring within the test vessels (i.e dissolved oxygen concentration, and TOC and/or COD) is reported;

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

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 source substance is difficult to test. Therefore the following additional information must be provided:

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

171 In studies (i) and (ii):

Reporting of the methodology and results

a) on the test procedure, you have not specified loading in number of *Daphnia* per litre and test medium composition in neither study (i) nor (ii);

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

c) water quality monitoring within the test vessels dissolved oxygen concentration, and TOC and/or COD) are not reported in the study (i) and TOC and/or COD is not reported in the study (ii);

d) the full record of the daily production of living offspring during the test [by each parent animal (semi-static test) in the study (i) /in each replicate (flow-through test) in study (ii) is not provided;

e) on the analytical method adequate information, i.e. performance parameters of the method are not reported in neither studies (i) nor (ii).;

f) No information is provided in the studies (i) and (ii).

172 Based on the above, the studies (i) and (ii) do not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 211 and the specifications of OECD GD 23. Therefore, the studies (i) and (ii) is not an adequate basis for your read-across predictions.

10.3. Assessment of the information provided in your comments

10.3.1. (Q)SAR adaptation (study iii) rejected

173 Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

(1) results need to be adequate for the purpose of risk assessment or classification and labelling, and
(2) adequate and reliable documentation of the method must be provided.

174 Regarding these conditions, we have identified the following issue:

10.3.1.1. Lack of justification of the representativeness of the structures

175 Under Guidance on IRs and CSA R.6.1.7.3. a prediction is adequate for the purpose of classification and labelling and/or risk assessment if the following conditions are met:

- the composition of the substance is clearly defined, and
- representative structure(s) for the assessment are selected.

176 Your registration dossier provides the following information:

- In Section 1.1. of your technical dossier, you define the Substance as an UVCB;
- In Section 1.2., you indicate that the Substance contains a high number of (unknown) branched isomers;

177 You have provided a prediction for the following structure:

- O=C(c1ccccc1C(=O)OCCC(C)CC(C)CCCC)OCCC(C)C(C)CCCCC

178 As already explained in the Section 0.1.1.2., you state that the Substance contains over two hundreds isomers but you do not provide detailed compositional information of the Substance (including information on isometric composition). Therefore, the Substance cannot be regarded as a well-defined substance.

179 In your comments, you state that "*due to its extremely low water solubility (ca. 0.004 µg/L), adsorptive properties (log Kow 10.3) and surface activity (surface tension 30.9 mN/m)*", no effects are expected at saturation. According to you, this is because above certain limits (i.e. logKow ≥5.0 for fish/ daphnia, logKow ≥ 6.4 for algae for acute effects, and logkow≥8 for chronic effects), empirical data indicate that the decreased solubility of lipophilic chemicals results in "*no effects at saturation*". ECHA acknowledges your comment. However, the Substance contains constituents of varying carbon chain length as well as isomers with varying degree of branching. Lower carbon-chain length and higher branching both lead to higher solubility and reduced lipophilicity. On this basis, you have not provided adequate justification that the selected structure (C9 including two methylation) and the log Kow estimate for the Substance (i.e., 10.3) are representative of the Substance as a whole (including its isomers with lower carbon number / higher degree of branching). On this basis, you fail to provide a justification as to why the selected structure can be regarded as representative of the Substance as a whole.

180 Therefore, you have not demonstrated that the prediction is adequate for the purpose of classification and labelling and/or risk assessment and adaptation is rejected.

181 Therefore, the information requirement is not fulfilled.

10.4. Study design and test specifications

182 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.

Reasons related to the information under Annex X of REACH

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

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

11.1. Information provided

184 In your dossier, you have not submitted any information for this requirement.

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

186 In the comments to the draft decision, you agree with ECHA's assessment. You "*plan to decide how to address this endpoint (read across vs experimental study) in a phased approach to testing*".

187 ECHA takes note of your intentions. You remain responsible for complying with this decision by the set deadline.

11.2. Specification of the study design

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

189 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).

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

References

The following documents may have been cited in the decision.

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

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

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

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

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

The information requirement for 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. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA 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.

In your comments to the draft decision, you requested an extension of the deadline to provide information from 36 to 48 months from the date of adoption of the decision.

You justify your request by possible delays due to limited capacity in the Contract Research Organizations (CRO). In addition, you argue that the extension is needed to proceed with the tiered testing strategy proposed by you in order to decide whether the request pre-natal study in rabbits can be covered by a read-across adaptation or whether a new study on the Substance should be conducted.

ECHA notes that you have not provided any documentary evidence to substantiate your request based on the limited capacity in the CRO. Secondly, the proposed tiered testing strategy relies on a read-across approach that has not yet been fully described and justified, as explained in in the Appendix on Reasons common to several requests above.

On this basis, ECHA has not modified the deadline to provide the information.

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,

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

- 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.

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.