~~Confidential~~

Helsinki, 22 January 2024

Addressee(s)
Registrant(s) of JS_26401-35-4 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
16 April 2021

Registered substance subject to this decision ("the Substance")
Substance name: Diisotridecyl adipate
EC/List number: 247-660-8

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 in requests 1.-5. below by ***27 October 2026*** and the information listed in the other requests below by ***27 October 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: Bacterial reverse mutation test, OECD TG 471 (2020)).

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

2. *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.

3. 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).

4. 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 5 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: OECD TG 407) by oral route, in rats.

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

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

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

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

7. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rat or rabbit, depending on the species tested in the first PNDT study requested above).

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 addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

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

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

Appendix 1: Reasons for the request(s)

Reasons common to several requests

0.1. Read-across adaptation rejected

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

- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- *In vitro* micronucleus study (Annex VIII, Section 8.4.2.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term repeated dose toxicity (28 day) (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study, one species (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study, second species (Annex X, Section 8.7.2.)

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

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

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

0.1.1. Predictions for toxicological properties

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

6 You predict the properties of the Substance from information obtained from the following source substance(s):

- bis(2-ethylhexyl) adipate, EC 203-090-1 (source substance 1);
- ditridecyl adipate, EC 241-029-0 (source substance 2).

7 You provide the following reasoning for the prediction of toxicological properties: *"Specifically, data from studies conducted on bis (2-ethylhexyl) adipate and […] ditridecyl adipate were used to fill the data gaps for diisotridecyl adipate. These substances are appropriate for read-across and a weight of evidence-approach because they are similar substances, based on their similar structure, toxicological and ecotoxicological profile useful for this interpolation.".*

8 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.

0.1.1.1. Read-across hypothesis contradicted by existing data

9 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 must 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.).

10 The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substance(s). An explanation why such differences do not affect the read-across hypothesis must be provided and supported by scientific evidence.

11 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar Substance and source substance(s) cause the same type of effect(s).

12 You predict no hazardous effects for the target and source substances but the study results related to mutagenicity, repeated dose toxicity and reproductive/developmental toxicity obtained with the source substance(s) vary and/or contradict your prediction for no hazardous effects.

13 *Mutagenicity*

14 Ambiguous results are reported with the source substance 1 in an *in vitro* chromosomal aberration study in mammalian cells (OECD TG 473, 1987) in the absence of metabolic activation.

15 *Repeated dose toxicity*

16 Test item related target organ toxicity effects are reported with the source substance 1 in a repeated dose 28-day oral toxicity study (OECD TG 407) provided in your dossier: increased renal and hepatic weight, hyaline and eosinophilic droplets in kidneys.

17 *Toxicity to reproduction or development*

18 Test item related reproductive/developmental toxic effects are reported with the source substance 1 in the following studies:

- a one-generation reproductive toxicity study (OECD TG 415, 1988): litter losses in treated groups, mean litter size reduced;
- a prenatal developmental toxicity study in rats (OECD TG 414, 1988): reduced ossification and increase in the incidence of visceral variants;
- a repeated dose 28-day oral toxicity study (OECD TG 407, 2006): increased ovarian follicle atresia and prolongation of the estrous stage.

19 In the comments to the draft decision, you argue that the above findings are incidental and you consider them as non-adverse or not toxicologically relevant. You also refer to additional studies with the source substance to support your overall conclusion on the absence of fertility effects and endocrine disruption properties of the source substance. However, the limited details provided in the dossier and in your comments on the protocols and results of these additional studies do not allow ECHA to assess the validity of your claims.

20 In addition, toxicokinetic studies in mice, rats and monkeys (1984) provided in your dossier show biotransformation of the source substance 1 into 2-ethylhexanoic acid (EC 205-743-6), a substance with a harmonised classification for developmental toxicity as Repr. 2 H361d (and as Repr. 1B H360D as of 23 November 2023, following the 18th ATP to Annex VI of the CLP Regulation).

21 The available set of data on the Substance and on the source substances indicates differences in the toxicological properties of the substances. This contradicts your read-

across hypothesis whereby the Substance and source substances cause the same type of effect(s). However, you have not supported and scientifically justified why such differences in the toxicological properties do not affect your read-across hypothesis.

0.1.1.2. Missing supporting information to compare properties of the substances(s)

22 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.).

23 Supporting information must include (e.g. bridging) hazard information and toxicokinetic information to compare properties of the target and source substances.

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

25 For the source substance 1, you provide the studies used in the prediction in the registration dossier. Apart from an Ames study (claimed equivalent to OECD TG 471, 1978), 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. In particular, you provided no toxicokinetic study on the target substance or study relevant to the adapted information requirements (bridging study) for mutagenicity, repeated dose toxicity, and reproductive and developmental toxicity.

26 In addition, specific reasons why these studies cannot be considered reliable are explained further below under the requests 1, 2, 3, 5, 6 and 7. Thus the data set reported in the technical dossier does not include relevant, reliable and adequate information for the target and source substance(s) to support your read-across hypothesis.

27 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 substance(s)

28 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.

29 Specific reasons why the studies on the target and source substances do not meet these criteria are explained further below under the applicable information requirement sections 1, 2, 3, 5, 6 and 7. Therefore, no reliable predictions can be made for these information requirements.

0.1.2. Conclusion

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

0.2. Weight of Evidence

31 Besides specifically claiming an adaptation using Annex XI, Section 1.5. (grouping of substances and read-across approach), you have indicated relying also on a weight-of-evidence approach. Annex XI, section 1.2 (Weight of Evidence) requires that adequate and reliable documentation is provided to describe your weight of evidence approach. You have however 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. ECHA understands therefore that you intend to adapt the information using Annex XI, Section 1.5. (grouping of substances and read-across approach) and has assessed the information on that basis.

Reasons related to the information under Annex VII of REACH

1. *In vitro* gene mutation study in bacteria

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

1.1. Information provided

33 You have provided:

(i) an *in vitro* gene mutation study (1978) with the Substance.

34 You have also 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:

(ii) an *in vitro* gene mutation study in bacteria (1996) with the source substance 1 bis(2-ethylhexyl) adipate (EC 203-090-1).

1.2. Assessment of the information provided

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

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

a) the test is performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101);
b) triplicate plating is used at each dose level;
c) the mean number of revertant colonies per plate is reported for the treated doses and the controls;
d) negative results are confirmed in a repeat experiment with modification of study parameters to extend the range of conditions assessed, or a justification why confirmation of negative results is not considered necessary is provided.

36 In study (i):

a) the test was performed with the strains *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98, TA 100 and Saccharomyces cerevisiae D4 (i.e. the strain *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is missing);
b) only single plating was not used at each dose level;
c) the mean number of revertant colonies per plate for the treated doses and the controls was not reported;
d) no repeat experiment was performed to confirm the negative results and no justification was provided.

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

38 Therefore, the information requirement is not fulfilled.

1.2.2. Read-across adaptation rejected

39 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.

1.2.2.1. Inadequate or unreliable study on the source substance(s)

40 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 471.

41 You considered study (ii) as unreliable (KL 4) because only three strains of bacteria were tested (S. typhimurium TA 1535, TA 1537, TA 98 and TA 100) and no details on the results for the treated and control groups are available.

42 Based on the above, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) required by the OECD TG 471.

43 Therefore, the information requirement is not fulfilled.

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

1.3. Study design

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

Reasons related to the information under Annex VIII of REACH

2. *In vitro* micronucleus study

46 An *in vitro* mammalian chromosomal aberration study or an *in vitro* mammalian micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

2.1. Information provided

47 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) an *in vitro* chromosomal aberration study in mammalian cells (1987) with the source substance 1 bis(2-ethylhexyl) adipate (EC 203-090-1).

2.2. Assessment of the information provided

2.2.1. Read-across adaptation rejected

48 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. Inadequate or unreliable study on the source substance(s)

49 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 473. Therefore, the following specifications must be met:

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

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

c) one positive control is included in the study;

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

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

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

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

h) to conclude on a negative outcome, a negative response is obtained in all three experimental conditions described in paragraph 28 of OECD TG 473, using a short-term treatment with and without metabolic activation and long-term treatment without metabolic activation.

50 In study (i), very limited details on the exact protocols and testing conditions used, and on the results obtained in the treated and control groups are provided and no comparison with the above specifications (a-h) of OECD TG 473 is possible.

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

52 Therefore, the information requirement is not fulfilled.

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

2.3. Study design

54 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).

2.3.1. Assessment of aneugenicity potential

55 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.

56 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).

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

57 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.

3.1. Triggering of the information requirement

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

59 The information for the *in vitro* gene mutation study in bacteria and for the in vitro mammalian chromosomal aberration study or *in vitro* mammalian micronucleus study provided in the dossier are rejected for the reasons provided in requests 1 and 2.

60 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.

61 Consequently, you are required to provide information for this information requirement, if the *in vitro* gene mutation study in bacteria and the *in vitro* micronucleus study provide negative results.

3.2. Information provided

62 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) an *in vitro* Mouse Lymphoma gene mutation study (OECD TG 476, 1988) with the source substance 1 bis(2-ethylhexyl) adipate (EC 203-090-1).

3.3. Assessment of the information provided

3.3.1. Read-across adaptation rejected

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

3.3.1.1. Inadequate or unreliable study on the source substance(s)

64 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 476 or the OECD TG 490 (Guidance on IRs and CSA, Table.7.7-2). Therefore, the following specifications must be met:

a) the maximum concentration tested induces 80-90% 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) the concurrent positive controls induce responses that are compatible with those generated in the historical positive control database and does not induce more than 90% of cytotoxicity compared to the negative control;

c) for the Mouse Lymphoma Assay (MLA), the concurrent positive control meets the acceptability criteria recommended by the MLA Expert Workgroup of the International Workshop for Genotoxicity Testing (IWGT) in terms of mutant frequency and/or small colony induction and described in paragraph 58 of OECD TG 490;

d) for the Mouse Lymphoma Assay (MLA), the concurrent negative control meets the acceptability criteria recommended by the MLA Expert Workgroup of the International Workshop for Genotoxicity Testing (IWGT) in terms of mutant frequency, cloning efficiency and suspension growth and described in paragraph 57 of OECD TG 490;

e) data on the cytotoxicity and the mutation frequency for the treated and control cultures are reported.

65 In study (i), very limited details on the cytotoxicity and mutant frequency results obtained in the treated and control groups are provided and no comparison with the above specifications (a-e) of OECD TG 476 or OECD TG 490 is possible.

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

67 Therefore, the information requirement is not fulfilled.

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

3.4. Study design

69 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.

4. Short-term repeated dose toxicity (28-day)

70 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.

4.1. Information provided

71 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-acute toxicity study (OECD TG 407, 2006) with the source substance 1 bis(2-ethylhexyl) adipate (EC 203-090-1).

4.2. Assessment of the information provided

4.2.1. Read-across adaptation rejected

72 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.

73 Therefore, the information requirement is not fulfilled.

74 In the comments to the draft decision, you acknowledge the data-gap.

4.3. Study design

75 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.

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

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

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

78 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 5).

79 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.

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

81 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 5; or
- a 28-day study as per the study design described in 4.3. in case the 90-day study is not requested in the adopted decision.

82 Your comments regarding your proposed alternative testing strategy are addressed in Appendix 2 to this decision.

Reasons related to the information under Annex IX of REACH

5. Sub-chronic toxicity study (90 days)

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

5.1. Information provided

84 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 source substance 1 bis(2-ethylhexyl) adipate (EC 203-090-1):

(i) a sub-chronic toxicity study (OECD TG 408, 1982) in rats;

(ii) a sub-chronic toxicity study (OECD TG 408, 1982) in mice;

(iii) a chronic toxicity study (1982) in rats;

(iv) chronic toxicity study (1982) in mice.

5.2. Assessment of the information provided

5.2.1. Read-across adaptation rejected

85 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.

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

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

a) body weight and food consumption is measured at least weekly;

b) 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;

c) haematological and clinical biochemistry tests are performed as specified in paragraphs 30-38 of OECD TG 408;

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

e) terminal organ and body weights are measured;

f) gross pathological examinations as specified in paragraphs 43-46 of OECD TG 408 are performed;

g) full histopathology is performed as specified in paragraphs 47-49 of OECD TG 408.

87 In the above studies:

a) body weight was only measured every four weeks in studies (iii) and (iv), and there is no information on how frequently food consumption was measured;

b) functional observation battery was not assessed. In particular, the following investigations are missing: sensory reactivity to stimuli of different types (e.g. auditory, visual and proprioceptive stimuli), assessment of grip strength and motor activity assessment;

c) haematology and clinical biochemistry were not performed;

d) oestrus cyclicity was not assessed;

e) terminal organ weights were not assessed and thus and organ/body weight ratios were not recorded;

f) organs for which the pathological examination was performed is missing in studies (i) and (ii);

g) organs for which the histopathological examination was perfomed is missing in studies (i) and (ii).

88 Based on the above, 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 OECD TG 408 and are not an adequate basis for your read-across predictions.

89 Therefore, the information requirement is not fulfilled.

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

5.3. Study design

91 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.

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

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

6. Pre-natal developmental toxicity study in one species

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

6.1. Information provided

95 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 pre-natal developmental toxicity study in rats (OECD TG 414, 1988) with the source substance 1 bis(2-ethylhexyl) adipate (EC 203-090-1).

6.2. Assessment of the information provided

6.2.1. Read-across adaptation rejected

96 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.

97 Therefore, the information requirement is not fulfilled.

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

6.3. Study design

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

100 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).

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

Reasons related to the information under Annex X of REACH

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

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

7.1. Information provided

103 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 pre-natal developmental toxicity study in rabbits (OECD TG 414, 2014) with the source substance 1 bis(2-ethylhexyl) adipate (EC 203-090-1).

7.2. Assessment of the information provided

7.2.1. Read-across adaptation rejected

104 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 study on the source substance(s)

105 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 414. Therefore, the following specifications must be met:

a) the highest dose level aims to induce toxicity or aims to reach the limit dose.

106 In study (i):

a) the highest dose level tested was 160 mg/kg bw/day, which is below the limit dose of the test guideline, and no adverse effect were observed. You indicate that this dose was selected based on dose range finding study. However, in this dose range finding study, severe maternal toxicity was noted at 300 mg/kg bw/day and no maternal toxicity was noted at 100 mg/kg bw/day. Therefore, limiting the highest dose to 160 mg/kg bw/day in the definitive study is questionable.

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

108 Therefore, the information requirement is not fulfilled.

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

7.3. Study design

110 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species, depending on the species tested in the first PNDT study (request 6 in this decision).

111 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).

112 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.

In the comments to the draft decision, you claim that ECHA forgot to include in the draft decision the information requirement for a screening study for reproductive/developmental toxicity (according to OECD TG 421 or 422) (Annex VIII, Section 8.7.1.) or did not give any reason for omitting it. However, as explained above, this information requirement is not addressed in this decision, because ECHA may later request the EOGRTS which will cover the same parameters.

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 11 August 2022.

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 but amended the deadline.

In your comments to the draft decision, you disagree with the deadlines for providing the requested studies due to the 6-month waiting time indicated by [redacted] laboratory and your intention to perform the requested studies in a sequential manner. In particular, you propose in your comments to conduct a combined 28-day repeated dose / reproductive and developmental toxicity screening study to adapt the higher-tier information requirements for repeated dose toxicity (90-day study) and reproductive and developmental toxicity (PNDT studies). Therefore, you argue that 30 months from the date of the decision are necessary for performing studies 1-4, 48 months for studies 5 and 6, and 72 months for study 7.

However, please note that the deadlines of the decision are set based on standard practice for carrying out OECD TG tests and complying with the studies as requested in the present decision. Your registration dossier is currently incompliant for the 90-day repeated dose toxicity study and the PNDT studies. You may still conduct the combined 28-day repeated dose / reproductive and developmental toxicity screening study at your own responsibility. However, ECHA cannot modify the deadlines to take into account your proposed testing-strategy because the 28-day repeated dose / reproductive and developmental toxicity screening study(ies) is not a legal prerequisite for conducting the 90-day repeated dose toxicity study and the PNDT studies.

The deadlines have already 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 has, however, extended the deadlines by another 6 months to 30 months for requests 1.-5. and 42 months for the other requests from the date of the decision, to take into account the evidence you provided with your comments for the longer laboratory waiting time.

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

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

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

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

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

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

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1 Test methods, GLP requirements and reporting

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

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

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

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

(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.

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

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