~~Confidential~~

Helsinki, 24 May 2024

Addressee
Registrant as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
07 August 2017

Registered substance subject to this decision ("the Substance")
Substance name: Bis(2-ethylhexyl) sebacate
EC/List number: 204-558-8

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 below by ***30 August 2027***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.):

   a. *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (EU B.71/OECD TG 442E)(Annex VII, Section 8.3.1.); and

   b. only if the *in vitro/in chemico* test methods specified under point a) 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: 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)

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

4. In vitro micronucleus study (Annex VIII, Section 8.4.2., test method: EU B.49./OECD TG 487)

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

6. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1., Column 2) based on request 9 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.) by oral route, to be combined with the screening for reproductive/developmental toxicity requested below

7. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

   However, in case the sub-chronic toxicity study (90 days) is not requested, EU B.64/OECD TG 422 is required.

8. Long-term toxicity testing on fish, also requested below (triggered by Annex VIII, Section 9.1.3., Column 2).

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

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

10. 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)

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

12. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210).

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)

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.:

- 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.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 have not provided a read-across justification document but ECHA understands you predict the properties of the Substance from information obtained from the following source substance:

- Bis(2-ethylhexyl) adipate, EC 203-090-1 (source substance).

6 You provide the following reasoning for the prediction based on toxicokinetic properties of diester substances (including the Substance and source substance): "*Metabolism of the diesters in animals would be expected to occur initially via enzymatic hydrolysis leading to the corresponding diacids [e.g. adipic and sebacic acids] and the corresponding linear or branched alcohols [e.g., 2-ethylhexyl alcohols]. These diacids and alcohols can be further metabolized or conjugated (e.g., glucuronides, sulfates, etc.) to polar products that are excreted in the urine*."

7 ECHA understands that your read-across hypothesis is based on the formation of common biotransformation products.

8 We have assessed this information and identified the following issues:

0.1.1.1. Absence of read-across documentation

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 include

an explanation why the properties of the Substance may be predicted from information on the source substance(s).

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

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

0.1.1.2. Missing supporting information on the formation of common compound

12 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.).

13 Supporting information must include toxicokinetic information on the formation of the common compound, supporting information on the rate of metabolism of the parent compounds and on the prediction on the impact of the exposure to the parent compound.

14 As indicated above, your read-across hypothesis is based on the biotransformation of the Substance and of the source substance to a common compound. In this context, information characterising the rate and extent of the biotransformation of the source substance is necessary to confirm the formation of the proposed common biotransformation product and to assess the impact of the exposure to the parent compounds.

15 However, you have not provided any experimental information about the biotransformation of the Substance nor the source substance to support your claims regarding formation of a common compound.

16 In the absence of this information, you have not provided supporting evidence establishing that the proposed common biotransformation product is formed as assumed in your read-across hypothesis. Therefore, you have not provided sufficient supporting information to scientifically justify your read-across hypothesis.

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

17 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.

18 Specific reasons why the studies on the source substance do not meet these criteria are explained further below under the applicable information requirement sections 1-2, 5-8,

and 10-11. Therefore, no reliable predictions can be made for these information requirements.

0.1.2. Conclusion

19 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. (Q)SAR adaptation rejected

20 You have adapted the following standard information requirements by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3.:

- 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.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Long-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1., column 2)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex VIII, Section 9.1.3, column 2)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

21 We have assessed this information and identified the following issues:

0.2.1. Predictions for toxicological properties

0.2.1.1. Lack of documentation of the model (QMRF)

22 Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and Guidance on IRs and CSA R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

23 You have not provided information about the model.

24 In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

0.2.1.2. Lack of documentation of the prediction (QPRF)

25 Guidance on IRs and CSA R.6.1.6.3. states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have

adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

26 You have not provided information about the prediction.

27 In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

0.2.1.3. The QSAR result is not equivalent to results obtained from the required experimental test

28 Results from (Q)SAR models are adequate for risk assessment or classification and labelling when they are equivalent to results obtained from the required experimental test. You have adapted the data requirement for the full in vitro genotoxicity battery and reproductive/developmental toxicity screening. The corresponding studies that must normally be performed for this particular information requirement are:

a) In vitro gene mutation study in bacteria (OECD TG 471);

b) In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (OECD TG 473/487);

c) In vitro gene mutation study in mammalian cells (OECD TG 476/490);

d) Screening for reproductive/developmental toxicity (OECD TG 421/422)

29 which measure:

a) gene mutations (point mutations and frameshifts) in bacterial cells;

b) structural and numerical chromosome aberrations mammalian cells;

c) gene mutations and structural chromosome aberrations in mammalian cells;

d) adverse effects on male and female sexual function and fertility, maternal post natal reproductive toxicity and offspring developmental toxicity.

30 You have provided the prediction from (Q)SAR models ACD/Percepta, Leadscope FDA Model Applier, Vega mutagenicity model and Toxtree which predict mutagenicity, genotoxicity on mouse lymphoma cells, chromosome aberration in vitro, potential of inducing chromosome aberration and micronucleus in vivo, and reproductive toxicity on male and female rats and mice.

31 It is not clear whether the applied models predict the specific required end-points of each test system, because the information provided is too broad or too vague (eg., 'mutagenicity' without explaining which elements of mutagenicity were covered; or 'potential of inducing chromosome aberration and micronucleus in vivo' without explaining how it is relevant for in vitro or, in case of column 2 adaptation, in which in vivo system this was tested) to determine whether it corresponds to the required measurement.

32 Thus, ECHA cannot establish that the all measurements of the corresponding studies for the endpoints have been considered. Therefore, the prediction is not adequate for the purpose of classification and labelling and/or risk assessment.

33 Therefore, the prediction is not adequate to meet the information requirement for endpoints a)-d) for the purpose of classification and labelling and/or risk assessment.

0.2.2. Predictions for ecotoxicological properties

0.2.2.1. Inadequate documentation of the prediction (QPRF)

34 ECHA Guidance R.6.1.6.3. states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint;
- a precise identification of the substance modelled;
- the relationship between the modelled substance and the defined applicability domain;
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

0.2.2.1.1. Long-term toxicity testing on aquatic invertebrates

35 You provided the following information about the prediction:

- the model prediction for daphnid 21-day Chronic Value (ChV);
- identification of the substance modelled, including EC number, name and SMILES notation of the Substance;
- your conclusion about the relationship between the modelled substance and the defined applicability domain: you report that the Substance is outside the applicability domain of the model.

36 The information you provided about the prediction lacks the following elements:

- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

0.2.2.1.2. Long-term toxicity testing on fish

37 You provided the following information about the prediction:

- the model prediction for fish 32/33-day Chronic Value (ChV);
- identification of the substance modelled, including EC number, name and SMILES notation of the Substance.

38 The information you provided about the prediction lacks the following elements:

- the relationship between the modelled substance and the defined applicability domain;
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

0.2.2.1.3. Assessment outcome

39 In absence of such information, ECHA cannot establish that the predictions for long-term toxicity testing on fish, and long-term toxicity testing on aquatic invertebrates can be used to meet the respective information requirements.

0.2.3. Conclusion on the (Q)SAR adaptation

40 Therefore, the information requirements are not fulfilled.

0.3. Weight of evidence adaptation requalified

41 Besides specifically claiming an adaptation using Annex XI, Section 1.5. (grouping of substances and read-across approach), you have indicated the adequacy of some of the endpoint study records as weight of evidence. 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. You have also flagged all these endpoint study records as unreliable without further explanation.

42 ECHA understands therefore you mention these studies as additional available information which is in line with the key information submitted like adaptation Annex XI, Section 1.5. (grouping of substances and read-across approach) but not as a separate adaptation.

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

43 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

44 You have provided:

(i) a rabbit occlusive patch test (1996) with the Substance;

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

(ii) an in vivo skin sensitisation test (1967) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

46 and furthermore, you have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(iii) a prediction using Toxtree decision rule system and Vega platform (2013).

1.2. Assessment of the information provided

1.2.1. Assessment whether the Substance causes skin sensitisation

1.2.1.1. The provided study does not meet the specification of the test guideline(s) (i)

47 To fulfil the information requirement, and to enable concluding whether the Substance causes skin sensitisation, a study must comply with the EU Method B.6/OECD TG 406 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the exposure conditions are described;
b) a dose level selection rationale is provided;
c) the induction concentration is the highest causing mild-to-moderate irritation to the skin;
d) the challenge dose is the highest non-irritation concentration;
e) a positive control is included to establish the sensitivity and reliability of the experimental technique.

48 The study (i) is described as an occlusive patch test in rabbits. Although the method used is not a guideline method (OECD or EU) due to the use of induction and challenge to assess topical reactions, it closely relates to Buehler Test (EU Method B.6/OECD TG 406).

49 However, the following specifications are not according to the requirements of OECD TG 406:

a) no details on exposure conditions were provided e.g. route of exposure, how many induction and challenge exposures there were and on which day(s), how many animals in treatment group;
b) no dose level selection rationale was provided;
c) the concentration used for induction was not specified and whether it caused

mild-to-moderate irritation;
d) the challenge concentration was not specified and whether it was the highest non-irritating concentration;
e) no information on positive control group was provided.

50 The information provided does not cover the specification(s) required by the OECD TG 406 and does not allow to make a conclusion whether the Substance causes skin sensitisation.

1.2.1.2. Read-across adaptation rejected

51 As explained in Section 0.1., your adaptation based on an analaogue read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issues addressed below.

1.2.1.2.1. Inadequate or unreliable studies on the source substance (ii)

52 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case EU Method B.6/OECD TG 406 (Article 13(3) of REACH. Therefore, the following specifications must be met:

a) a dose level selection rationale is provided;
b) the induction concentration is the highest causing mild-to-moderate irritation to the skin and the challenge dose is the highest non-irritation concentration;
c) positive and negative controls are included to establish the sensitivity and reliability of the experimental technique.

53 In study (ii):

a) no dose level selection rationale was provided;
b) the concentration used for induction and challenge were the same indicating that it cannot be both i.e. concentration cause mild to moderate irritation and the highest non-irritating concentration;
c) no information on positive and negative control groups were provided.

54 Based on the above, the study does not provide an adequate and reliable coverage of the key parameters of OECD TG 406 and does not allow to make a conclusion whether the Substance causes skin sensitisation.

1.2.1.3. (Q)SAR adaptation rejected (iii)

55 As explained in Section 0.2., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

1.2.2. No assessment of potency

56 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).

57 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.

58 Therefore, the information requirement is not fulfilled.

1.3. Study design

59 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.

60 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated in vitro/in chemico 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

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

2.1. Information provided

62 You have provided:

(i) an in vitro gene mutation study in bacteria (1996) with the Substance;

63 and in addition, you have adapted this information requirement by using Annex XI, Section 1.5. (Grouping of substances and read-across approach) based on the following experimental data from the source substance;

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

64 and furthermore, you have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(iii) a prediction using ACD/Percepta, Leadscope FDA Model Applier and Vega mutagenicity model (2013).

2.2. Assessment of the information provided

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

65 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) at least 5 doses are evaluated, in each test condition; triplicate plating is used at each dose level;

c) concurrent strain-specific positive controls, both with and without metabolic activation, are included in each assay and the number of revertant colonies per plate induced by the positive controls demonstrates the effective performance of the assay;

d) a concurrent negative control is included in each assay and the number of revertant colonies per plate for the concurrent negative control is inside the historical control range of the laboratory;

e) data on type and composition of metabolic activation system are reported:

f) the mean number of revertant colonies per plate is reported for the treated doses and the controls;

g) 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.

66 In study (i):

a) the test was performed with the strains on *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (i.e., the 5th strain *S. typhimurium* TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is missing;

b) one dose was reported in absence and in presence of metabolic activation (i.e., less than 5 doses) and no data on whether triplicate plating was used is provided;

c) concurrent strain-specific positive controls were not included in the study;

d) a concurrent negative control was not included in the study:

e) data on type and composition of metabolic activation system were not reported;

f) the mean number of revertant colonies per plate for the treated doses and the controls was not reported;

g) no repeat experiment was performed to confirm the negative results and no justification was provided.

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

2.2.2. Read-across adaptation rejected

68 As explained in Section 0.1., your adaptation based on analogue read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issues addressed below.

2.2.2.1. Inadequate or unreliable studies on the source substance (ii)

69 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed/cover an exposure duration comparable to or longer than the one specified in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 471. Therefore, the following specifications must be met:

a) two separate test conditions are assessed: in absence of metabolic activation and in presence of metabolic activation;

b) 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);

c) at least 5 doses are evaluated, in each test condition; triplicate plating is used at each dose level;

d) concurrent strain-specific positive controls, both with and without metabolic activation, are included in each assay and the number of revertant colonies per plate induced by the positive controls demonstrates the effective performance of the assay;

e) a concurrent negative control is included in each assay and the number of revertant colonies per plate for the concurrent negative control is inside the historical control range of the laboratory;

f) the mean number of revertant colonies per plate is reported for the treated doses and the controls;

g) 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.

70 In study (ii):

a) metabolic activation was used but data on type and composition of metabolic activation system are missing;

b) the test was performed with the strains on *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (i.e., the 5th strain *S. typhimurium* TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101 is missing*);*

c) one dose was reported in absence and in presence of metabolic activation (i.e., less than 5 doses) and no data on whether triplicate plating was used is provided;

d) concurrent strain-specific positive controls were not included in the study;

e) a concurrent negative control was not included in the study;

f) the mean number of revertant colonies per plate for the treated doses and the controls was not reported;

g) no repeat experiment was performed to confirm the negative results and no justification was provided.

71 Based on the above, the study do not provide an adequate and reliable coverage of the key parameters specified in the OECD TG 471. Therefore these studies are not an adequate basis for your read-across predictions.

2.2.3. (Q)SAR adaptation rejected (iii)

72 As explained in Section 0.2., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

73 Therefore, the information requirement is not fulfilled.

2.3. Study design

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

3. Long-term toxicity testing on aquatic invertebrates

75 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

76 In section 4.8 of your registration dossier, you provide a reference to a handbook ([redacted], 2013) and on the basis of this source, you report that the Substance is not soluble in water.

77 The Substance's water solubility is 2.026e-5 mg/L on the basis of Wskowwin (v1.42) prediction, using the SMILES notation and melting point reported in the registration dossier. In your registration dossier, you have reported a value of 1.5e-7 mg/L.

78 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

79 The information provided, its assessment and the specifications of the study design are addressed under request 11.

Reasons related to the information under Annex VIII of REACH

4. In vitro micronucleus study

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

4.1. Information provided

81 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 source substance:

(i) an *in vitro* chromosomal aberration test (1987) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1

(ii) *an in vitro* chromosomal aberration test (1993) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1

(iii) a sister chromatid exchange assay in mammalian cells (1987) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1

(iv) a sister chromatid exchange assay in mammalian cells (1993) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

82 and furthermore, you have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(v) a prediction on mouse lymphoma gentoxicity using ACD/Percepta and Leadoscope (2013)

(vi) a prediction on the potential of inducing chromosome aberrations in vitro using ACD/Percepta and Leadoscope (2013)

(vii) a prediction on the potential of inducing chromosome aberrations in vivo in rodents using Leadscope FDA Model Applier and ACD/Percepta (2013)

(viii) a prediction on the potential of inducing micronulei in vivo in rodents using ACD/Percepta and Leadscope FDA Model Applier and the Toxtree decision rule system (2013).

4.2. Asessment of the information provided

4.2.1. Read-across adaptation rejected

83 As explained in Section 0.1., your adaptation based on an analogue read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issues addressed below.

4.2.1.1. Inadequate or unreliable studies on the source substance (i and ii)

84 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3). To fulfil the information requirement, the study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test conducted in mammalian cells. The study must comply with the OECD TG 473 or the OECD TG 487, respectively (Article 13(3) of REACH). Therefore, the following specifications must be met:

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

b) at least 3 concentrations are evaluated, in absence and in presence of metabolic activation;

c) data on type and composition of metabolic activation system are reported;

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

e) positive and negative controls are included in the study;

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

85 In studies (i and ii):

a) no dose selection rationale is reported ie. whether tested concentration induced 55+5% of cytotoxicity compared to the negative control, or precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL;

b) one test concentration (i.e., less than 3 concentrations) was reported in absence and in presence of metabolic activation;

c) data on type and composition of metabolic activation system were not reported;

d) no data on how many metaphases were scored was reported;

e) no positive or negative controls were included in the study;

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

4.2.1.2. Study not adequate for the information requirement (iii and iv)

86 Toxicological studies must comply with a recognised test method (Article 13(3) of REACH), in this case an in vitro chromosomal aberration test or an in vitro micronucleus test, conducted in mammalian cells and comply with with the OECD TG 473 or the OECD TG 487. Such study must cover the key parameters of the corresponding OECD test guideline (Article 13(3) of REACH).

87 The studies (iii) and (iv) are described as a sister chromatid exchange assay in mammalian cell. This study is not an in vitro cytogenicity study in mammalian cells nor an in vitro micronucleus study.

88 The information provided does not cover the key parameter(s) required by the OECD TG 473/487.

4.2.2. (Q)SAR adaptation rejected (v, vi, vii, viii)

89 As explained in Section 0.2., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

90 Therefore, the information requirement is not fulfilled.

4.3. Study design

91 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the in vitro mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the in vitro mammalian

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

4.3.1. Assessment of aneugenicity potential

92 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.

93 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)).

94 [1] According to the TG 487 (2016) 'At the present time, no aneugens are known that require metabolic activation for their genotoxic activity' (paragraph 34).

5. In vitro gene mutation study in mammalian cells

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

5.1. Triggering of the information requirement

96 Your dossier contains read-across and (Q)SAR adaptations for an in vitro gene mutation study in bacteria, and for an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study. In addition, your dossier contains negative results for an Ames test with the Substance.

97 The information for the in vitro gene mutation study in bacteria and for the in vitro cytogenicity study in mammalian cells or in vitro micronucleus study provided in the dossier are rejected for the reasons provided in requests 2 and 4.

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

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

5.2. Information provided

100 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 (1982) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

(ii) an in vitro gene mutation study in mammalian cells (1988) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1.

5.3. Assessment of the information provided

5.3.1. Read-across adapatation rejected

101 As explained in Section 0.1., your adaptation based on an analogue read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issues addressed below.

5.3.1.1. Inadequate or unreliable studies on the source substance (i and ii)

102 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case the OECD TG 476 or the OECD TG 490 (Guidance on IRs and CSA, Table.7.7-2) (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) two separate test conditions are assessed: in absence of metabolic activation and in presence of metabolic activation;

b) 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;

c) a positive and a negative control is included in the study;

d) 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;

e) data on type and composition of metabolic activation system are reported;

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

103 In studies (i) and (ii):

a) the test was performed in the presence of metabolic activation but data on type and composition of metabolic activation system are missing;

b) for study (i) the maximum tested concentration did not induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL;

c) no positive or negative controls were included in the studies;

d) the performance of positive and negative controls in not reported;

e) data on type and composition of metabolic activation system were not reported;

f) data on the cytotoxicity and the mutation frequency for the treated and control cultures were not reported.

104 Based on the above, the studies do not provide an adequate and reliable coverage of the key parameters specified in the OECD TG 476/490. Therefore these studies are not an adequate basis for your read-across predictions.

105 Therefore, the information requirement is not fulfilled.

5.4. Study design

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

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

107 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.

6.1. Information provided

108 You have provided the following study:

(i) a three week oral repeated dose hepato-toxicity study in rats (2003) with the Substance

6.2. Assessment of the information provided

6.2.1. Inadequate or unreliable studies provided (i)

109 You have provided an unreliable study (i) with the Substance that you have assigned a reliability score 4 according to Klimisch et al. (1997). This study is not evaluated for hazard indentification and therefore, the information requirement is not fulfilled.

6.3. Study design

110 When there is no information available neither for the 28-day repeated dose toxicity (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

111 The study design is addressed in request 7.3.

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

112 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 9).

113 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.

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

115 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 9; 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.

7. Screening study for reproductive/developmental toxicity

116 A screening study for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1.

7.1. Information provided

117 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 one generation reproduction toxicity study ([redacted], 1988) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

(ii) a one generation reproduction toxicity study ([redacted], 1988) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

118 and additionally, you have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(iii) a prediction on mouse and rat male and female reproductive toxicity using Leadscope FDA Model Applier.

7.2. Assessment of the information provided

7.2.1. Read-across adaptation rejected

119 As explained in Section 0.1., your adaptation based on an analogue read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issues addressed below.

7.2.1.1. Inadequate or unreliable studies on the source substance (i and ii)

120 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case the EU B.63/OECD TG 421 or EU B.64/OECD TG 422 (Article 13(3) of REACH). Therefore, the following specifications must be met:

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

b) at least 10 male and 12-13 female animals are included for each dose and control group;

c) body weights are measured at least weekly;

d) food consumption is measured at least weekly;

e) the nature, severity, and duration of clinical signs observed daily are reported;

f) thyroid hormone levels are measured;

g) terminal organ and body weights are reported;

h) gross pathology of reproductive organs is performed, and the presence or absence, incidence and severity of abnormalities is evaluated;

i) histopathology of reproductive organs and tissues is performed, and the presence or absence, incidence and severity of abnormalities is evaluated.

j) parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition and lactation are reported;

k) oestrous cycles are monitored;

l) offspring parameters such as number and sex of pups/stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/nipple retention in male pups are reported.

121 In study (ii)

a) only two dose levels and no concurrent controls were described;

122 In studies (i) and (ii)

b) the number of animals per sex per group is not reported;

c) data on body weights, body weight changes are missing;

d) data on food consumption are missing;

e) data on clinical signs, including their nature, severity, and duration, are not reported;

f) thyroid hormone levels were not measured;

g) terminal organ weights and organ/body weight ratios are not reported;

h) data on gross pathology findings, including incidence and severity of abnormalities, are not reported;

i) data on histopathology findings, including incidence and severity of abnormalities, are not reported;

j) data on parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition and lactation are missing;

k) data on oestrous cycles is missing;

l) data on number and sex of pups/stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/nipple retention in male pups is missing.

123 Based on the above, the studies do not provide an adequate and reliable coverage of the key parameters specified in the OECD TG 421/422. Therefore these studies are not an adequate basis for your read-across predictions.

7.2.2. (Q)SAR adaptation rejected (iii)

124 As explained in Section 0.2., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

125 Therefore, the information requirement is not fulfilled.

7.3. Study design

126 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

127 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex VIII, Section 8.7.1., Column 1).

128 Therefore, the study must be conducted in rats with oral administration of the Substance.

129 When there is no information available neither for the 28-day repeated dose toxicity study (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided (Guidance on IRs and CSA, Section R.7.6.2.3.2.)

130 In case the adopted decision no longer contains a request for a sub-chronic (90 days) study (e.g. as a result of an overall tonnage band change of the joint submission), a study according to the test method EU B.64/OECD TG 422 must be performed in rats.

131 The information requirement for the 28-day repeated dose toxicity study is not fulfilled for the reasons explained under request 6.

8. Long-term toxicity testing on fish

132 Short-term toxicity testing on fish is an information requirement under Annex VIII, Column 1, Section 9.1.3. However, long-term toxicity testing on fish may be required by the Agency (Section 9.1.3., Column 2) if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

8.1. Triggering of the information requirement

133 As already explained in request 3, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

8.2. Information requirement not fulfilled

134 The information provided, its assessment and the specifications of the study design are addressed under request 12.

Reasons related to the information under Annex IX of REACH

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

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

9.1. Information provided

136 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 toxicity study (1980) in the rat with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

(ii) a sub-chronic toxicity study (1980) in the mouse with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

(iii) a sub-chronic toxicity study (1951) in the rat with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

(iv) a sub-chronic toxicity study (1997) in the rat with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1;

(v) a sub-chronic toxicity study (1997) in the mouse with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1.

9.2. Assessment of the information provided

9.2.1. Read-across adaptation rejected

137 As explained in Section 0.1., your adaptation based on an analogue read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issues addressed below.

9.2.1.1. Inadequate or unreliable studies on the source substance (i, ii, iii, iv, v)

138 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed/cover an exposure duration comparable to or longer than the one specified in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 408. 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 10 male and 10 female animals are used for each concentration and control group;

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

d) 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;

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

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

g) terminal organ and body weights are measured;

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

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

139 The read-across studies provided (i, ii, iii, iv, v) do not meet the above specifications:

a) no concurrent controls are described (i, ii, iii, iv, v);

b) sex and number of the study animals:

- number of animals per sex per group not specified: (iii);
- only females were included in each test group: (iv, v);

c) there is no information on how frequently body weights and food consumption were measured (iii, iv, v);

d) description for monitoring of clinical signs and the assessment of functional observations is missing: (i, ii, iii, iv, v);

e) haematology and clinical biochemistry were not performed: (i, ii, iii, iv, v);

f) oestrus cyclicity was not assessed: (i, ii, iii, iv, v);

g) terminal organ weights and organ/body weight ratios:

- not recorded: (i, ii);
- recorded only for liver, kidneys, spleen, and testis: (iii);
- recorded only for liver: (iv, v);

h) gross pathological examination:

- data for organs for which the examination was performed is missing: (i, ii);
- examination only for liver, kidneys, spleen, and testis: (iii);
- examination only for liver: (iv, v);

i) histopathological examination:

- data for organs for which the examination was performed is missing: (i, ii);
- examination only for liver, kidneys, spleen, and testis: (iii);
- examination only for liver: (iv, v).

140 Based on the above, the studies do not provide an adequate and reliable coverage of the key parameters specified in the OECD TG 408. Therefore these studies are not an adequate basis for your read-across predictions.

141 Therefore, the information requirement is not fulfilled.

9.3. Study design

142 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.

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

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

10. Pre-natal developmental toxicity study in one species

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

10.1. Information provided

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

(i) a teratogenicity study in the rat (1988) with the source substance Bis(2-ethylhexyl) adipate, EC 203-090-1.

10.2. Assessment of the information provided

10.2.1. Read-across adaptation rejected

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

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

148 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed/cover an exposure duration comparable to or longer than the one specified in the corresponding test method referred to in Article 13(3), in this case OECD TG 414. Therefore, the following specifications must be met:

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) body weight and food consumption are measured at least every three days;

e) the nature, severity, and duration of the clinical signs are observed daily;

f) the dams are examined for any structural abnormalities, weight and histopathology of the thyroid gland, thyroid hormone measurements, gravid uterus weight, and uterine content;

g) the foetuses are examined for body weight, number and percent of live and dead foetuses and resorptions, sex ratio, external, skeletal and soft tissue alterations (variations and malformations), measurement of anogenital distance in all live rodent foetuses;

149 In study (i):

a) only two dose levels and no concurrent control group were included;

b) the number of animals per group is not reported;

c) the exposure duration is not reported;

d) data on body weights, body weight changes and food consumption are missing;

e) data on clinical signs, including nature and severity, are missing

f) data on the examination of the dams, including incidence and severity, are missing

g) data on the examination of the foetuses, including incidence and severity, are missing;

150 Based on the above, the studies do not provide an adequate and reliable coverage of the key parameters specified in the OECD TG 408. Therefore these studies are not an adequate basis for your read-across predictions and the information requirement is not fulfilled.

10.3. Study design

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

152 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).

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

11. Long-term toxicity testing on aquatic invertebrates

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

11.1. Information provided

155 You have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(i) a prediction from ECOSAR v1.11 (2013);

(ii) a data waiver, with the following justification: "*In accordance with column 2 of REACH annex IX, further degradation testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation*".

11.2. Assessment of the information provided

11.2.1. (Q)SAR adaptation rejected

156 As explained in Section 0.2., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

11.2.2. Your justification to omit the study has no legal basis

157 A registrant may only adapt this information requirement based on the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.1., does not allow omitting the need to submit information on long-term aquatic toxicity under Column 1 (Decision of the Board of Appeal in case A-011-2018).

158 Your justification to omit this information listed under point (ii) does not refer to any legal ground for adaptation under Annex XI to REACH.

159 Therefore, the information requirement is not fulfilled.

11.3. Study design

160 The Substance is difficult to test due to the low water solubility (1.5e-7 mg/L mg/L) . 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 211. 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 solutions.

12. Long-term toxicity testing on fish

161 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

12.1. Information provided

162 You have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(i) a prediction from ECOSAR v1.11 (2013);

(ii) a data waiver, with the following justification: "*In accordance with column 2 of REACH annex IX, further degradation testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation*".

12.2. Assessment of the information provided

12.2.1. (Q)SAR adaptation rejected

163 As explained in Section 0.2., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

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

12.2.1.1. Inappropriate measures of robustness of the model

165 The Guidance on IRs and CSA R.6.1.3. states that for (Q)SAR models, to be scientifically valid, i.e. condition (1), they must fulfil the principles listed in the OECD Principles for (Q)SAR validation (ENV/JM/MONO(2007)2). The fourth of these principles requires that a model has appropriate measures of the internal performance (i.e. goodness-of-fit and robustness) and predictivity.

166 A model is considered robust when it is built from a training set which includes a sufficient number of substances. The minimum number of substances depends on the number of variables or descriptors included in the model. The ratio between the number of substances and the number of variables or descriptors must be at least 5.

167 The training set of your model is based on 1 descriptor and 4 chemicals.

168 Since the ratio between the number of substances and the number of variables or descriptors is less than five in version 1.11 of ECOSAR (Class-specific estimations: Esters), you have not established the robustness, and thus the scientific validity, of the model.

12.2.2. Your justification to omit the study has no legal basis

169 A registrant may only adapt this information requirement based on the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.1., does not allow omitting the need to submit information on long-term toxicity to fish under Column 1 (Decision of the Board of Appeal in case A-011-2018).

170 Your justification to omit this information listed under point (ii) does not refer to any legal ground for adaptation under Annex XI to REACH.

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

172 Therefore, the information requirement is not fulfilled.

12.3. Study design

173 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

174 OECD TG 210 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" under request 11.

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 (2022).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2023).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2023).
Appendix to Chapter R.7c for nanomaterials; ECHA (2023).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2023).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2023).
Guidance on intermediates; ECHA (2010).
All Guidance on REACH is 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

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 24 April 2023.

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

ECHA did not receive any comments within the commenting period.

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 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 Annexes VII, VIII and IX to REACH, for registration at 100-1000 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 (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

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

(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 all constituents of each Test Material and their concentration values.

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).