~~Confidential~~

Helsinki, 24 May 2024

Addressees
Registrants of JS_6938-94-9_SSS as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
23 February 2019

Registered substance subject to this decision ("the Substance")
Substance name: diisopropyl adipate
EC/List number: 230-072-0

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. Surface tension (Annex VII, Section 7.6.; test method: EU A.5./OECD TG 115)

2. Skin sensitisation (Annex VII, Section 8.3.)

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

   b) only if the *in vitro/in chemico* test methods specified under point a) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429).

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

4. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

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

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

6. *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.

7. 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).

8. 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

9. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203)

10. Adsorption/desorption screening (Annex VIII, Section 9.3.1.; test method: EU C.18/OECD TG 106 or EU C.19/OECD TG 121)

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

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

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

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

14. Long-term toxicity 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 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. Weight of evidence adaptation rejected

1 ECHA understands that you have adapted the following standard information requirements by using Annex XI, Section 1.2. (weight of evidence):

- *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 toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

2 In addition, based on your comments to the draft decision, ECHA understands that you have adapted the following standard information requirements by using Annex XI, Section 1.2. (weight of evidence):

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90 days), oral route (Annex IX, Section 8.6.2.)

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

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

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

0.1.1. Lack of documentation justifying the weight of evidence adaptation

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

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

8 Beside this critical deficiency common to all information requirements under consideration, your weight of evidence approach has additional deficiencies.

9 Additional deficiencies that are specific for each of the information requirements individually are addressed under request(s) 3, 4, 6, 7, 8, 11 and 13.

10 Additional common deficiencies are identified below.

0.2. Read-across adaptation rejected

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

12 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.

13 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.

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

0.2.1. Predictions for toxicological properties

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

(i) Dibutyl adipate EC 203-350-4

(ii) Adipic Acid EC 204-673-3

(iii) Diisobutyl adipate EC 205-450-3

(iv) 3-methylbutyl isovalerate EC 211-536-1

(v) Isoamyl Propionate EC 203-322-1

16 In the comments to the draft decision you provide a read-across justification (Appendix 1, Parts A, B and C) to adapt the information requirements for the following standard information requirements:

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

17 Based on the read-across justification provided, you predict the properties of the Substance from information obtained from the following two source substance(s):

(i) Dibutyl adipate, EC 203-350-4

(vii) Bis(2-ethylhexyl)adipate, EC 203-090-1

18 You provide the following reasoning for the prediction of toxicological properties: *"different compounds are supposed to cause the same type of effects as a result of structural similarity*." More in particular you indicate that"*experimental and predicted data show that the physicochemical profiles of the target and source substances are comparable […] The*

side carbon chains in these substances influence water solubility, and there is a decreasing trend along with the increasing length of carbon chains among these substances. The comparable physicochemical properties indicate that the differences in the side carbon chains do not significantly influence physicochemical properties.". In addition, you state that

19 *"the available in vivo studies with the source substances indicate a similar toxicological profile to the target substance. […]. Experimental data obtained with the target and source substances indicate low oral and dermal acute toxicity."*

20 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 substances.

0.2.1.1. Deficiencies of the read-across approach related to the information requests on reproductive and repeated dose toxicity

0.2.1.1.1. Read-across hypothesis contradicted by existing data

21 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.).

22 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 to be provided and supported by scientific evidence.

23 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar Substance and source substances cause the same type of effects.

24 However, based on the information in the read-across justification provided in your comments (Annex 1, Part A, B and C, 2.8. Data Matrix), you report water solubilities of

a. 500-1000 mg/L at 26° for the Substance;
b. 35 mg/L at 25 °C for the source substance (i) (EC 203-350-4) and
c. <0.005 mg/L @ 22°C for source substance (vii) (EC 203-090-1).

25 For acute oral toxicity you report an

d. LD50=5000 mg/kg/bw for the Substance;
e. LD50=12900 mg/kg/bw for the source substance (i) (EC 203-350-4) and
f. LD50=45000mg/kg/bw for source substance (vii) (EC 203-090-1).

26 The available set of data on the Substance and on the source substances indicates differences in the physicochemical and toxicological properties of the substances. This contradicts your read-across hypothesis whereby the Substance and source substances cause the same type of effects. However, you have not supported and scientifically justified why such differences in the physicochemical and toxicological properties do not affect your read-across hypothesis.

0.2.1.1.2. QSAR Toolbox outcome is considered a read-across and not a QSAR

27 In your comments to the draft decision, you have provided in-silico information derived from data from the Substance and source substances to further support your read-across approach which assumes that different compounds have the same type of effects, using the OECD QSAR Toolbox for the following information requirements:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90 days), oral route (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.

28 As the substances (EC 203-350-4 and EC 203-090-1) are used as source substances to predict the properties of the Substance, we understand that you have adapted the standard information requirements under Annex XI, Section 1.5 of REACH (grouping and read-across).

29 Therefore, ECHA has evaluated the provided in-silico data under the read-across approach and thus the deficiencies of the read-across approach identified under section 0.2 apply similarly to the in silico-data that is provided.

0.2.1.2. Deficiencies of the read-across approach related to the information requests on mutagenicity

0.2.1.2.1. Absence of justification for use of information on source substances

30 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must include a an explanation why the properties of the Substance may be predicted from information on the source substance(s).

31 You have provided robust study summaries for the studies conducted with other substances than the Substance in order to comply with the REACH information requirements.

32 However, you have not provided documentation to explain why this information is relevant for the Substance and why the properties of the Substance may be predicted from information on the source substances

33 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance(s).

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

34 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.). Supporting information must include studies to compare properties of the Substance and the source substance(s) which are relevant to the adapted information requirement, to confirm your read-across prediction.

35 As indicated above, you did not provide a read-across hypothesis. However, 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 studies of comparable design and duration with the Substance and the source substances.

36 You have provided an in vitro gene mutation study in mammalian cells with the Substance. No information with the Substance has been provided for in vitro gene mutation study in bacteria or in vitro cytogenicity study in mammalian cells.

37 An in vitro gene mutation study in mammalian cells is considered complementary to a gene mutation study in bacteria and it is not intended to supersede the gene mutation study in bacteria as both studies investigate different mechanisms of gene mutation.

38 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.

0.2.2. Predictions for ecotoxicological properties

0.2.2.1. Aquatic toxicity

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

(ii) Adipic Acid, EC 204-673-3;

(vi)N-butyl 4-oxopentanoate, EC 218-143-4;

(vii) Bis(2-ethylhexyl)hexanedioate, EC 203-090-1.

0.2.2.1.1. Absence of read-across documentation

40 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).

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

42 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance(s).

43 Therefore, the information requirement is not fulfilled.

0.2.3. Deficiencies of the read-across approach related to information requests on human health and ecotoxicological properties

0.2.3.1. Inadequate or unreliable source studies

44 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.

45 Specific reasons why the studies on the source substance(s) do not meet these criteria are explained further below under the applicable information requirement in sections 4, 11, 12 and 13. Therefore, no reliable predictions can be made for these information requirements.

0.2.4. Conclusion on the read-across approach

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

Reasons related to the information under Annex VII of REACH

1. Surface tension

47 Surface tension of an aqueous solution is an information requirement under Annex VII to REACH (Column 1 of Section 7.6).

1.1. Information provided

48 You have adapted this information requirement by using Annex XI, Section 1.3. (Qualitative or Quantitative Structure-Activity Relationships, (Q)SARs). To support the adaptation, you have provided the following information:

(i) a prediction from ACD/Labs' ACD/PhysChem Suite (2012).

49 ECHA has assessed the provided information and identified the following issues.

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

50 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. The corresponding study that must normally be performed for this particular information requirement is the OECD TG 115, OECD harmonized ring method, which measures: the surface tension (i.e. the free surface enthalpy per unit of surface area) of the test substance in an aqueous solution, the concentration of which should be 90% of the saturation solubility of the test substance, or 1 g/L, whichever of the two is lower.

51 You have provided the prediction from a (Q)SAR model (ACD/PhysChem Suite), which predicts the surface tension of test substance.

52 The model predicts the surface tension of the pure form of the test substance and does not measure the surface tension of the test substance in an aqueous solution at a concentration prescribed by the Test Guideline. Therefore, the prediction is not adequate to meet the information requirement for the surface tension of an aqueous solution endpoint, for the purpose of classification and labelling and/or risk assessment.

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

2. Skin sensitisation

54 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).

2.1. Information provided

55 You have adapted this information requirement by using Annex XI, Section 1.3. (Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(i) a prediction from Danish QSAR DB (2018);

(ii) Human Repeat Insult Patch Tests (HRIPT) (1989) with the Substance.

2.2. Assessment of the information provided

2.2.1. Assessment whether the Substance causes skin sensitisation

2.2.1.1. (Q)SAR adaptation rejected

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

(1) the prediction needs to be derived from a scientifically valid model,

(2) the substance must fall within the applicability domain of the model,

(3) results need to be adequate for the purpose of risk assessment or classification and labelling, and

(4) adequate and reliable documentation of the method must be provided.

2.2.1.1.1. Inadequate documentation of the prediction (QPRF)

57 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:

(1) the relationship between the modelled substance and the defined applicability domain;

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

58 You provided the following information about the prediction: "negative in domain" predictions by four different models (i.e, Leadscope, Battery, SciQSAR and CASE Ultra). The consensus result was given by the Battery model from the Danish QSAR Database.

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

(1) details to independently verify that the substance falls within the applicability domain as described in the QMRF of the models,

(2) information on analogues, and how their predicted and experimental data supports the prediction.

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

61 Based on the above, your QSAR adaptation under Annex XI, Section 1.3. is rejected.

62 On this basis, the information provided does not contribute to the assessment whether the Substance causes skin sensitisation.

2.2.1.2. Adequacy of the provided study for hazard identification

63 A study must be adequate for the corresponding information requirement. According to the Guidance on IRs and CSA, Section R.4 (page 1), "The evaluation of data quality includes assessment of adequacy of the information for hazard/risk assessment and C&L purposes". The Guidance on IRs and CSA, Section R.4 (page 1) defines adequacy as "the usefulness of data for hazard/risk assessment purposes". As a consequence, a study must be relevant for hazard assessment and for classification and labelling purposes.

64 You have provided a study (ii) according to Human Repeat Insult Patch Test (HRIPT) and you consider that the Substance is not a skin sensitiser based on the studies. The studies are conducted using concentrations 3 % or lower.

65 The study (ii) appears to have been designed to establish safe levels for specific intended uses in cosmetic products rather than to investigate the intrinsic properties of the Substance

as required for the purpose of hazard identification. In particular, the dose levels used in this study are low for hazard identification purposes and the method in question is intended to confirm the absence of irritation and sensitisation potential. Therefore, the study does not allow to make a conclusion whether the Substance causes skin sensitisation.

66 Therefore, the studies (ii) are rejected and do not allow to make a conclusion whether the Substance causes skin sensitisation.

2.2.2. No assessment of potency

67 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).

68 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 2.2.1. above), this condition cannot be assessed.

69 Therefore, the information requirement is not fulfilled.

2.3. Study design

70 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.

71 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.

72 In the comments to the draft decision, you agree to perform the requested study following the "2 out of 3" Defined Approach in OECD 497 and perform two in vitro studies with the Substance. You indicate that if the Substance gets classified as Cat 1 based on the two in vitro studies, a third in vitro study will be performed to determine if the Substance should be classified as Cat 1A, 1B or remain as Cat 1 if the data on potency is inconclusive. ECHA agrees with your intended testing strategy. ECHA notes, that in case inconclusive results are obtained from the in vitro strategy for either hazard identification (skin sensitiser or not) or with respect to potency categorisation (Cat 1A vs 1B), in vivo testing is required under Section 8.3.2, Column 2.

3. *In vitro* gene mutation study in bacteria

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

3.1. Information provided

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

(i) an *in vitro* gene mutation study in bacteria (1984) with the source substance (iv) (EC 211-536-1)

(ii) an *in vitro* gene mutation study in bacteria (2018) with the source substance (i) (EC EC 203-350-4)

3.2. Assessment of the information provided

3.2.1. Weight of evidence adaptation rejected

75 As explained in Section 0.1., your adaptation based on weight of evidence under Annex XI, Section 1.2. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

3.2.1.1. Missing robust study summaries

76 Annex XI, Section 1.2. requires that whenever weight of evidence is used adequate and reliable documentation of the applied method must be provided. Such documentation must include a robust study summary for each source of information used in the adaptations.

77 A robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

78 In addition, for weight of evidence adaptations, the robust study summary must clearly indicate which key parameters of the study normally required for the information requirement are investigated in the study.

79 For the sources of information (i) and (ii) you have provided the outcomes of the studies but you have not provided detailed information on the results in tabulated form, allowing for an independent assessment of each source of information and contributing to the overall weight of evidence for the information requirement under consideration.

80 In the absence of complete robust study summary, including the tabulated results, these sources and the reliability of their contribution on these parameters to your weight of evidence adaptations cannot be evaluated.

81 ECHA concludes that you have failed to provide a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.2.

82 Consequently, sources of information that are lacking robust study summaries cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration.Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for in vitro gene mutation study in bacteria.

83 Based on the above, your weight of evidence adaptation under Annex XI, Section 1.2. is rejected.

84 Therefore, the information requirement is not fulfilled.

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

3.3. Study design

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

4. Short-term toxicity testing on aquatic invertebrates

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

4.1. Information provided

88 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) and Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a short-term toxicity study on *Daphnia magna* (2014) with source substance vi.,, EC 218-143-4;

(ii) a short-term toxicity study on *Daphnia magna* (2018) with source substance vii., EC 203-090-1;

(iii) a short-term toxicity study on *Daphnia magna* (2018) with source substance ii., EC 204-673-3.

4.2. Assessment of the information provided

4.2.1. Read-across adaptation rejected

89 As explained in Section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

4.2.1.1. Studies not conducted according to GLP

90 (Eco)toxicological studies must comply with GLP or another recognised international standard; Art. 13(4) of REACH.

91 You have indicated that studies (i), (ii), and (iii) are "not GLP-compliant", without further explanation.

92 The tests do not comply with GLP or another recognised international standard and is therefore rejected.

4.2.1.2. Inadequate or unreliable studies on the source substances

93 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 202. Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

b) the test duration is 48 hours or longer;

Characterisation of exposure

c) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;

Reporting of the methodology and results

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

e) the number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation;

f) the dissolved oxygen and pH measured at least at the beginning and end of the test is reported.

94 In study (i):

Technical specifications impacting the sensitivity/reliability of the test

a) the test duration was 24 hours;

Characterisation of exposure

b) no analytical monitoring of exposure was conducted

Reporting of the methodology and results

c) on the test design, you have not specified the nominal concentrations that were tested: you only report the nominal concentrations as "0-360 mg/L" and that the study was not a limit test;

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

e) the dissolved oxygen measured at least at the beginning and end of the test is not reported.

95 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the test duration of study (i) was shorter than that prescribed by OECD TG 202 and the exposure concentrations were not measured. Both deviations may have resulted in the underestimation of the measured effect concentration of source substance vi.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported key pieces of information (e.g. dissolved oxygen, number of immobilised daphnids after 24 and 48 hours for each treatment group and control) that are relevant to the validity of the study. Because of this, ECHA cannot independently verify if study (i) is valid.

96 On this basis, the specifications of OECD TG 202 are not met.

97 In study (ii):

Characterisation of exposure

b) no analytical monitoring of exposure was conducted

Reporting of the methodology and results

c) on the test design, you have not specified the nominal concentrations that were tested;

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

e) the dissolved oxygen and pH measured at least at the beginning and end of the test is not reported.

98 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically the exposure concentrations were not measured. This deviation may have resulted in the underestimation of the measured effect concentration of source substance vii.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported key pieces of information (e.g. dissolved oxygen concentrations, number of immobilised daphnids after 24 and 48 hours for each treatment group and control) that are relevant to the validity of the study. Because of this, ECHA cannot independently verify if study (ii) is valid.

99 On this basis, the specifications of OECD TG 202 are not met.

100 In study (iii):

Characterisation of exposure

b) no analytical monitoring of exposure was conducted

Reporting of the methodology and results

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

e) the dissolved oxygen and pH measured at least at the beginning and end of the test is not reported.

101 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically, the exposure concentrations were not measured. This deviation may have resulted in the underestimation of the measured effect concentration of source substance ii.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported key pieces of information (e.g. dissolved oxygen concentrations, number of immobilised daphnids after 24 and 48 hours for each treatment group and control) that are relevant to the validity of the study. Because of this, ECHA cannot independently verify if study (iii) is valid.

102 On this basis, the specifications of OECD TG 202 are not met.

103 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 and/or cover an exposure duration comparable to or longer than the one specified in the corresponding OECD TG.

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

105 Therefore, this information requirement is not fulfilled.

4.2.2. Weight of evidence adaptation rejected

106 As explained in Section 0.1., your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

107 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information based on which a conclusion on the information requirement can be drawn.

108 Information that can be used to support weight of evidence adaptation for the information requirement of Annex VII, Section 9.1.1. includes similar information that is produced by the OECD TG 202. OECD TG 202 requires the study to investigate the following key parameter:

- the concentration of the test material leading to the immobilisation of 50% of daphnids at the end of the test is estimated;

109 As explained above, studies (i), (ii), and (iii) are rejected.

110 Because of this, you have provided no sources of information that are adequate for fulfilling the information requirement of short-term toxicity testing on aquatic invertebrates, as part of a weight of evidence adaptation under Annex XI, Section 1.2. Therefore, this information requirement is not fulfilled.

111 In your comments to the draft decision, you agree with ECHA's assessment. Instead of performing a new OECD TG 202 study as requested, you propose to perform the long-term toxicity to aquatic invertebrates study (OECD TG 211; see request 13) on the Substance.

112 Annex VII, Section 9.1.1, Column 2 specifies that the short-term toxicity study does not need to be conducted if a long-term aquatic toxicity study on invertebrates is available.

113 At present, no compliant long-term toxicity study on aquatic invertebrates is provided in the registration dossier, therefore no conclusion on the compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

5. Growth inhibition study aquatic plants

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

5.1. Information provided

115 You have provided:

(i) Growth inhibition study on algae (2014) with the Substance.

5.2. Assessment of the information provided

5.2.1. Study not conducted according to GLP

116 (Eco)toxicological studies must comply with GLP or another recognised international standard; Article 13(4) of REACH.

117 You have indicated that study (i) is "not GLP-compliant", without further explanation.

118 The test does not comply with GLP or another recognised international standard and is therefore rejected.

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

119 To fulfil the information requirement, a study must comply with OECD TG 201 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;

Characterisation of exposure

b) analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;

Reporting of the methodology and results

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

120 In study (i):

Technical specifications impacting the sensitivity/reliability of the test

a) the number of replicates was 2 in each test concentration;

Characterisation of exposure

b) no analytical monitoring of exposure was conducted;

Reporting of the methodology and results

c) tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

121 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the number of replicates was lower than that prescribed by OECD TG 201. This deviation may have affected the measured effect concentration of the Substance.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported key pieces of information (e.g. algal biomass for each treatment group and control determined in each flask at least daily) that are relevant to the validity of the study. Because of this, ECHA cannot independently verify if study (i) is valid.

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

123 Therefore, the information requirement is not fulfilled.

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

Reasons related to the information under Annex VIII of REACH

6. *In vitro* micronucleus study

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

6.1. Information provided

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

(i) an *in vitro* chromosomal aberration study (1984) with the source substance (iv) (EC 211-536-1);

(ii) an *in vitro* chromosomal aberration study (1984) with the source substance (v) (EC 203-322-1).

6.2. Assessment of the information provided

6.2.1. Weight of evidence adaptation rejected

127 As explained in Section 0.1., your adaptation based on weight of evidence under Annex XI, Section 1.2. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

6.2.1.1. Incomplete robust study summaries

128 Annex XI, Section 1.2. requires that whenever weight of evidence is used adequate and reliable documentation of the applied method must be provided. Such documentation must include a robust study summary for each source of information used in the adaptations.

129 A robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

130 In addition, for weight of evidence adaptations, the robust study summary must clearly indicate which key parameters of the study normally required for the information requirement are investigated in the study.

131 For the sources of information (i) and (ii) you have provided the outcomes of the studies but you have not provided detailed information on the results in tabulated form, allowing for an independent assessment of each source of information and contributing to the overall weight of evidence for the information requirement under consideration.

132 In the absence of complete robust study summaries, including the tabulated results, these sources and the reliability of their contribution on these parameters to your weight of evidence adaptations cannot be evaluated.

133 ECHA concludes that you have failed to provide a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.2.

134 Consequently, sources of information that are lacking robust study summaries cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration.

135 Beside these critical deficiencies, ECHA has also assessed the other aspects of your adaptation.

6.2.1.1. Two separate test conditions

136 Information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.4.3. includes similar information that is produced by the OECD TG 473. OECD TG 473 requires the study to investigate the following key parameter(s):

(1) two separate test conditions are assessed: in absence of metabolic activation and in presence of metabolic activation

137 None of the information sources provide information on the test conditions in presence of metabolic activation.

138 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for in vitro micronucleus study.

139 Based on the above, your weight of evidence adaptation under Annex XI, Section 1.2. is rejected.

140 Therefore, the information requirement is not fulfilled.

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

6.3. Study design

142 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).

6.3.1. Assessment of aneugenicity potential

143 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.

144 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).

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

145 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.

7.1. Triggering of the information requirement

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

147 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 3 and 6.

148 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.

149 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.

7.2. Information provided

150 ECHA understands that you have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following:

(i) an *in vitro* gene mutation study in mammalian cells (2015) with the Substance;

7.3. Assessment of the information provided

7.3.1. Weight of evidence adaptation rejected

151 As explained in Section 0.1., your adaptation based on weight of evidence under Annex XI, Section 1.2. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

7.3.2. Only one source of information

152 Annex XI, Section 1.2 states that there may be sufficient weight of evidence "from several independent sources of information".

153 You have only provided one source of information.

154 Irrespective of this deficiencies, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided source of information and found the following deficiency.

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

155 To fulfil the information requirement, a study must comply with 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) 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 produce a statistically significant increase compared with the concurrent negative control;

c) sufficient number of cells to be plated was 10 E6 cells according to the OECD TG 476 dated 1997 (applicable at the time of study (i)) or never less than 2 x 10 E6 since OECD TG 476 adopted in 2016.

156 In study (i):

a) 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;

b) the positive control with metabolic activation was reported to be invalid as it did not produce any increase in the response (number of colonies) while the positive control without metabolic activation produced an increase in the response (no statistical analysis possible because of the value -zero- of the negative control);

c) low number of cells was used in the study because the number of cells plated was 5 x 10 E5 whereas the OECD TG dated 1997 and 2016 both require higher number of cells to be used.

157 The information provided does not cover the specification(s) required by the OECD TG 476.

158 Therefore, the information requirement is not fulfilled.

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

7.4. Study design

160 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.

8. Screening for reproductive/developmental toxicity

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

8.1. Information provided

162 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 substances:

(i) a pre-natal developmental toxicity study (1973) with the Substance;
(ii) a sub-acute toxicity toxicity study (2014) with the Substance;
(iii) a screening for reproductive/developmental toxicity study (1996) with the source substance (i) (EC 203-350-4).

163 In addition in your comments to the draft decision you provide experimental data from the following source substance:

(iv) a one-generation reproductive toxicity study (1983) with the source substance (vii) (EC 203-090-1)

8.2. Assessment of the information provided

8.2.1. The available study is not reliable – study (i)

164 Under Annex VIII, Section 8.7., Column 2, the study does not need to be conducted if a pre-natal developmental toxicity study (OECD TG 414) referred to in Annex IX, Section 8.7.2. is available.

165 The study (i) is a pre-natal developmental toxicity study.

166 However, for the reasons explained in request 12 the study (i) is not reliable.

167 Based on the above, your adaptation is rejected.

8.2.2. Inadequate or unreliable study (ii)

168 To fulfil the information requirement, a study must comply with 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) the exposure duration is at least four weeks for males, including a minimum of two weeks prior to mating, and approximately 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation;
b) offspring parameters such as number and sex of pups, stillbirths and live births, gross abnormalities, pup body weight, litter weight are reported.

169 In study (ii):

a) the exposure duration was 28 days for males and females (i.e., less than 63 days for females), without mating the animals in the study at all;
b) data on number and sex of pups, stillbirths and live births, gross abnormalities, pup body weight, litter weight is missing.

170 Study (ii) does not provide an adequate and reliable coverage of the specifications required by the OECD TG 421/422.

8.2.3. Weight of evidence adaptation rejected – studies (iii, iv)

171 As explained in Section 0.1., your adaptation based on weight of evidence under Annex XI, Section 1.2. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

8.2.3.1. Incomplete robust study summaries (iv)

172 Annex XI, Section 1.2. requires that whenever weight of evidence is used adequate and reliable documentation of the applied method must be provided. Such documentation must include a robust study summary for each source of information used in the adaptations.

173 A robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

174 In addition, for weight of evidence adaptations, the robust study summary must clearly indicate which key parameters of the study normally required for the information requirement are investigated in the study.

175 For the source of information (iv) you have provided the outcomes of the studies but you have not provided detailed information on the results in tabulated form, allowing for an independent assessment of each source of information and contributing to the overall weight of evidence for the information requirement under consideration.

176 In the absence of complete robust study summaries, including the tabulated results, these sources and the reliability of their contribution on these parameters to your weight of evidence adaptations cannot be evaluated.

177 ECHA concludes that you have failed to provide a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.2.

178 Consequently, sources of information that are lacking robust study summaries cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration.

8.2.4. Read-across adaptation rejected - studies (iii, iv)

179 As explained in Section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

180 Based on the above, the studies are not an adequate basis for your read-across predictions.

181 Therefore, the information requirement is not fulfilled.

8.3. Study design

182 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.

183 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).

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

9. Short-term toxicity testing on fish

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

9.1. Information provided

186 You have provided:

(i) a short-term toxicity study on fish (2013) with the Substance.

9.2. Assessment of the information provided

9.2.1. Study not conducted according to GLP

187 (Eco)toxicological studies must comply with GLP or another recognised international standard; Article 13(4) of REACH.

188 You have indicated that study (i) is "not GLP-compliant", without further explanation.

189 The test does not comply with GLP or another recognised international standard and is therefore rejected.

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

190 To fulfil the information requirement, a study must comply with OECD TG 203 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Validity criteria

a) the analytical measurement of test concentrations is conducted;

Technical specifications impacting the sensitivity/reliability of the test

b) the fish-to-water loading rate is ≤ 0.8 g of fish (wet weight) per litre of water for static and semi-static tests;

c) the water temperature is adequate for the selected test species;

Characterisation of exposure

d) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available.

191 In study (i):

Validity criteria

a) no analytical measurement of test concentrations was conducted;

Technical specifications impacting the sensitivity/reliability of the test

b) the test was conducted using a static setup and the fish-to-water loading rate was 1 g of fish (wet weight) per litre of water;

c) the test was conducted on *Danio rerio* and the test water temperature was 29°C;

Characterisation of exposure

d) no analytical monitoring of exposure was conducted.

192 Based on the above,

- the validity criteria of OECD TG 203 are not met
- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the test was conducted at a higher temperature (29°C) and at a higher fish-to-water loading rate (1 g/L) than the ranges recommended in OECD TG 203 (21-25°C and ≤ 0.8 g/L, respectively). These deviations from OECD TG 203 may have impacted the reliability of the measured effect concentration.

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

194 Therefore, the information requirement is not fulfilled.

195 In your comments to the draft decision, you agree with ECHA's assessment. Instead of performing a new OECD TG 203 study as requested, you propose to perform the long-term fish toxicity study (OECD TG 210; see request 14) on the Substance.

196 Annex VIII, Section 9.1.3, Column 2 specifies that the short-term fish toxicity study does not need to be conducted if a long-term aquatic toxicity study on fish is available.

197 At present, no long-term toxicity study on fish is provided in the registration dossier, therefore no conclusion on the compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

10. Adsorption/ desorption screening

198 Adsorption/desorption screening is an information requirement under Annex VIII to REACH (Section 9.3.1).

10.1. Information provided

199 You have provided:

(i) an adsorption/desorption screening study (2016) with the Substance;

10.2. Assessment of the information provided

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

200 To fulfil the information requirement, a study must comply with the OECD TG 121 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Key parameter to be measured

a) Coverage of the key parameter which is the adsorption coefficient Koc as determined by the partition of the test material between the mobile solvent phase and the cyanopropyl stationary phase using reverse phase HPLC;

Technical specifications impacting the sensitivity/reliability of the test

b) The solid phase consists of cyanopropyl chemically bound resins (e.g. Hypersil and Zorbax CN) chemically bound onto silica;

c) The mobile phase consists of one of the following two options: methanol/water (55/45% v/v) or methanol/0.01M citrate-buffer pH 6.0 (55/45% v/v).

201 In study (i):

Key parameter to be measured

a) The adsorption coefficient K_{oc}, as determined by the partition of the test material between the mobile solvent phase and the cyanopropyl stationary phase using reverse phase HPLC, was not determined;

Technical specifications impacting the sensitivity/reliability of the test

b) The solid phase consisted of ZORBAX Eclipse Plus C18 where the stationary phase is C18 (i.e. a solid phase that has different chemical composition than what is specified in the test guideline);

c) The mobile phase consisted of acetonitrile : water (55:45).

202 Based on the above,

- the key parameter of OECD TG 121 is not covered
- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the study does not meet the technical specifications of OECD TG 121 and it is not reliable because the key parameter (adsorption coefficient K_{oc} as determined by the partition of the Substance between the mobile solvent phase and the cyanopropyl stationary phase using reverse phase HPLC) was not measured as indicated.

203 On this basis, the specificationss of OECD 121 are not met.

204 Therefore, the information requirement is not fulfilled.

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

10.3. Study design

206 To fulfil the information requirement, the test methods according to OECD TG 106 or 121 are in general appropriate. You can choose any of these methods, but you must ensure that the Substance is within the applicability domain of the chosen test method.

Reasons related to the information under Annex IX of REACH

11. Sub-chronic toxicity study (90 days)

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

11.1. Information provided

208 You have provided:

(i) a sub-acute toxicity study (2014) with the Substance.

209 In addition, based on your comments to the draft decision, ECHA understands that you have adapted this requirement by using Annex XI, Section 1.2. (weight of evidence) and Annex XI, Section 1.5. (grouping and read-across). With your comments you provide the experimental data from the following source substance:

(ii) a 2-year chronic toxicity study (1982) with the source substance (vii) (EC 203-090-1).

11.2. Assessment of the information provided

11.2.1. Study not adequate for the information requirement (i)

210 To fulfil the information requirement, a study must comply with the OECD TG 408 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the exposure duration is at least 90 days.

211 In study (i):

a) the exposure duration was only 28 days.

212 The information provided does not cover the specification(s) required by the OECD TG 408.

11.2.2. Weight of evidence adaptation rejected – studies (i, ii)

213 As explained in Section 0.1., your adaptation based on weight of evidence under Annex XI, Section 1.2. is rejected.

11.2.3. Read-across adaptation rejected - study (ii)

214 As explained in Section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

11.2.3.1. Inadequate or unreliable studies on the source substance

215 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 be normally 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) haematological and clinical biochemistry tests are performed as specified in paragraphs 30-38 of OECD TG 408.

216 In study (ii):

a) only two dose levels were described;

b) haematology and clinical biochemistry were not performed.

217 The information provided does not cover the specification(s) required by the OECD TG 408.

218 Based on the above, the study does no provide an adequate and reliable coverage of the key parameters of the OECD TG 408. Therefore this study is not an adequate basis for your read-across adaptation.

219 Therefore, the information requirement is not fulfilled.

11.3. Study design

220 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.

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

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

12. Pre-natal developmental toxicity study in one species

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

12.1. Information provided

224 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 pre-natal developmental toxicity study in rat (1973) with the Substance;

(ii) a pre-natal developmental toxicity study in rat (2006) with the source substance (ii) (EC 204-673-3);

(iii) a pre-natal developmental toxicity study in mouse (2006) with the source substance (ii) (EC 204-673-3);

(iv) a pre-natal developmental toxicity study in rabbit (2006) with the source substance (ii) (EC 204-673-3);;

(v) a pre-natal developmental toxicity study in rat (1973) with the source substance (iii) (EC 205-450-3);

(vi) a pre-natal developmental toxicity study in rat (1973) with the source substance (i) (EC 203-350-4);

(vii) a screening for reproductive/developmental toxicity study in rat (1996) with the source substance (i) (EC 203-350-4).

225 In addition in comments to the draft decision you provide the experimental data from the following source substance:

(viii) a pre-natal developmental toxicity study in rat (1991) with the source substance (vii) (EC 203-090-1);

12.2. Assessment of the information provided

12.2.1. Read-across adaptation rejected

226 As explained in Section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

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

227 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 be normally 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;

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

c) the (daily) 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 (not for rabbits), thyroid hormone measurements (not for rabbits), 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);

h) the route of administration is oral if the substance is a solid or liquid. A justification is provided in case of deviations (Annex IX, Section 8.7.2.).

i) the foetuses are examined (for sex and body weight, and external, skeletal and soft tissue alterations (variations and malformations)), and examinations for number of resorptions and/or live foetuses.

228 In studies (ii), (iii) and (iv):

a) the highest dose levels tested was 288, 263 and 250 mg/kg bw/day, respectively, which is below the limit dose of the test guideline, and no adverse effect were observed, and no justification for the dose setting;

229 In studies (ii) to (vi):

b) only 5 females were included in each test and control group;

In studies (v) and (vi)

c) the exposure duration was insufficient as administration was on gestation days 5, 10 and 15 only, not daily;

In studies (ii) to (vi)

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;

h) The route of administration was not oral despite the substance being a liquid and no justification for the deviation was provided.

230 The study (vii) is a screening test rather than a conclusive developmental toxicity study:

i) The foetuses are not examined (for sex and body weight, and external, skeletal and soft tissue alterations (variations and malformations)), and no examinations for number of resorptions and/or live foetuses are not investigated/anogenital distance is not measured in live rodent foetuses.

231 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), and/or cover an exposure duration comparable to or longer than the one specified in the corresponding OECD TG.

12.2.2. The provided study (i) does not meet the specifications of the test guideline(s) and Annex IX, Section 8.7.2.

232 To fulfil the information requirement, a study must comply with OECD TG 414 (Article 13(3) of REACH) and Annex IX, Section 8.7.2. Therefore, the following specifications must be met:

a) at least 20 female animals with implantation sites for each test and control group are included;
b) the exposure duration is at least from implantation until one day prior to scheduled caesarean
c) body weight and food consumption are measured at least every three days;
d) the nature, severity, and duration of the clinical signs are observed daily;
e) the dams are examined for any structural abnormalities, weight and histopathology of the thyroid gland, thyroid hormone measurements, gravid uterus weight, and uterine content;
f) 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;
g) The route of administration is oral if the substance is a solid or liquid. A justification is provided in case of deviations (Annex IX, Section 8.7.2.).

233 In study (i):

a) only 5 females were included in each test and control group;
b) the exposure duration was insufficient as administration was on gestation days 5, 10 and 15 only, not daily;
c) data on body weights, body weight changes and food consumption are missing;
d) data on clinical signs, including nature and severity, are missing;
e) data on the examination of the dams, including incidence and severity, are missing;
f) data on the examination of the foetuses, including incidence and severity, are missing;
g) The route of administration was not oral despite the substance being a liquid and no justification for the deviation was provided.

234 The information provided does not cover the specification(s) required by the OECD TG 414.

12.2.3. Test material not representative of the Substance – study (i)

235 To comply with this information requirement, the test material in a study must be representative for the Substance; Article 10 and Recital 19 of REACH; Guidance on IRs and CSA, Section R.4.1.

236 The study (i) is a reference to data from handbook or collection of data. The public reference states that the studies have been conducted with "*seven adipates (dimethyl, diethyl, dipropyl, diisobutyl, di-n-butyl, di-2-ethylhexyl, and dicyclohexyl)*." Your study record in IUCLID refers to diisopropyl adipate as the test material.

237 ECHA cannot therefore rule out the possibility that test (i) has been conducted with a read-across substance instead of the Substance. In the absence of full documentation of the reference study (i) specifying the identity of the test material, ECHA considers the test material not representative for the Substance.

238 Therefore, the information requirement is not fulfilled.

12.3. Study design

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

240 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).

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

13. Long-term toxicity testing on aquatic invertebrates

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

13.1. Information provided

243 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, version 1.11– Class-specific estimations: Esters (2012).

244 In addition, 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:

(ii) a long-term toxicity study on *Daphnia magna* (2018) with source substance vii., EC 203-090-1;

(iii) a long-term toxicity study on *Daphnia magna* (2018) with source substance ii., EC 204-673-3.

13.2. Assessment of the information provided

13.2.1. (Q)SAR adaptation rejected

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

(1) the prediction needs to be derived from a scientifically valid model,

(2) the substance must fall within the applicability domain of the model,

(3) results need to be adequate for the purpose of risk assessment or classification and labelling, and

(4) adequate and reliable documentation of the method must be provided.

13.2.1.1. Inadequate documentation of the prediction (QPRF)

246 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.

247 In prediction (i), you provided the following information about the prediction: the precise identification of the substance modelled (including numerical identifiers, name, SMILES notation of the predicted structure) and a numerical value for the model prediction. 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.

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

249 Based on the above, your QSAR adaptation under Annex XI, Section 1.3. is rejected.

13.2.2. Read-across adaptation rejected

250 As explained in Section 0.2, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

13.2.2.1. Inadequate or unreliable studies on the source substances

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

Reporting of the methodology and results

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

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

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

d) water quality monitoring within the test vessels (i.e. pH, temperature and dissolved oxygen concentration, and TOC and/or COD and hardness where applicable) is reported;

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

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

252 In study (ii):

Reporting of the methodology and results

a) on the test design, you have not specified the test type (e.g. semi-static or flow-through);

b) on the test procedure, you have not specified the test medium composition;

c) the nominal test concentrations are not reported;

d) water quality monitoring within the test vessels (including pH, temperature, and dissolved oxygen concentration) are not reported;

e) the number of deaths among the parent animals (if any) and the day on which they occurred is not reported;

f) regarding the analytical method, you have not specified if analytical monitoring was conducted.

253 Based on the above,

- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported key pieces of information, including information relevant to the characterisation of exposure and information relevant to validity criteria. Because of this, the available information is not sufficient for ECHA to conduct an independent assessment of the validity of study (ii).

254 On this basis, the specifications of OECD TG 211 are not met.

255 In study (iii):

Reporting of the methodology and results

b) on the test procedure, you have not specified the test medium composition;

d) water quality monitoring within the test vessels (including pH, and dissolved oxygen concentration) are not reported;

e) the number of deaths among the parent animals (if any) and the day on which they occurred is not reported;

f) the results of the analytical determination of exposure concentrations provided are not reported.

256 Based on the above,

- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported key pieces of information, including information relevant to the characterisation of exposure and information relevant to validity criteria. Because of this, the available information is not sufficient for ECHA to conduct an independent assessment of the validity of study (iii).

257 On this basis, the specifications of OECD TG 211 are not met.

258 Based on the above, studies (ii) and (iii) submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameter(s) of the corresponding OECD TG.

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

260 Therefore, the information requirement is not fulfilled.

13.2.3. Weight of evidence adaptation rejected

261 As explained in Section 0.1., your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

262 Information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 9.1.5. includes similar information that is produced by the OECD TG 211. OECD TG 211 requires the study to investigate the following key parameters:

a) the concentrations of the test material leading to no observed effect (NOECs) on the following parameters:

- the reproductive output of Daphnia sp. expressed as the total number of living offspring produced per parental animal at the end of the test, and
- the survival of the parent animals during the test.

263 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information based on which a conclusion on the information requirement can be drawn.

264 As explained above, studies (i), (ii), and (iii) are rejected.

265 Because of this, you have provided no sources of information that is adequate for fulfilling the information requirement of long-term toxicity testing on aquatic invertebrates, as part of a weight of evidence adaptation under Annex XI, Section 1.2.

266 Therefore, this information requirement is not fulfilled.

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

14. Long-term toxicity testing on fish

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

14.1. Information provided

269 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, version 1.11 – Class-specific estimations: Esters (2018).

14.2. Assessment of the information provided

14.2.1. (Q)SAR adaptation rejected

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

(1) the prediction needs to be derived from a scientifically valid model,

(2) the substance must fall within the applicability domain of the model,

(3) results need to be adequate for the purpose of risk assessment or classification and labelling, and

(4) adequate and reliable documentation of the method must be provided.

14.2.1.1. Inappropriate measures of robustness of the model

271 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.

272 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.

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

274 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.

14.2.1.2. Inadequate documentation of the prediction (QPRF)

275 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.

276 You provided the following information about the prediction: the precise identification of the substance modelled (including numerical identifiers, name, SMILES notation of the predicted structure) and a numerical value for the model prediction. 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.

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

14.3. Conclusion

278 Based on the above, your QSAR adaptation under Annex XI, Section 1.3. is rejected.

279 Therefore, the information requirement is not fulfilled.

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

14.4. Study design

281 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.).

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

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 10 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 request(s) or the deadline.

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 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;

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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/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 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).