~~Confidential~~

Helsinki, 12 June 2023

Addressees
Registrant(s) of EC417-310-0_Fructalate as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
16/04/2019

Registered substance subject to this decision ("the Substance")
Substance name: diethyl 1,4-cyclohexanedicarboxylate
EC/List number: 417-310-0

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 the deadline of ***19 December 2025***.

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

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

1. 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

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

2. 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)

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

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

The reasons for the decision(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.

In the requests above, the same study has been requested under different Annexes. This is because some information requirements may be triggered at lower tonnage band(s). In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band(s).

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 decision
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 decision

Contents

0. Reasons common to several requests

0.1. Assessment of the read-across approach

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

i. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

ii. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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

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

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

0.1.1. Predictions for toxicological properties

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

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

i. dimethyl cyclohexane-1,4-dicarboxylate, EC No. 202-347-5

7 You provide the following reasoning for the prediction of toxicological properties: ” Having compared disseminated dossiers on ECHA website for the above-mentioned compounds, ethanol and methanol are not expected to be metabolites of significant importance for the repeat dose toxicity or developmental and reproductive toxicity endpoints. Therefore, only Cyclohexane-1,4-dicarboxylic acid was assessed in this document.”

8 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance based on a worst-case approach.

9 We have identified the following issue(s) with the prediction(s) of toxicological properties:

0.1.2. Missing supporting information

10 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.).

11 Supporting information must include bridging studies to compare properties of the Substance and source substances.

12 As indicated above, your read-across hypothesis is based on the assumption that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance. In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm a conservative prediction of the properties of the Substance from the data on the source substance(s). Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and for the source substance(s).

13 You have not provided reproductive toxicity or developmental toxicity data on the Substance.

14 For the source substance, you provide the studies used in the predictions for reproductive toxicity and developmental toxicity.

15 Your read-across justification or the registration dossier does not currently include any studies for the Substance that would confirm a conservative prediction of the reproductive or developmental toxic properties of the Substance.

16 In the absence of such information, you have not established that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance. Therefore, you have not provided sufficient supporting information to scientifically justify the read-across.

17 In your comments to the draft decision you state that "although a bridging study between the target and source substances is missing for the reprotoxicity endpoint, other studies are available demonstrating similar toxicity between the two substances." However, as already explained above, bridging data relevant to the adapted information requirement is required to compare the related properties of the Substance and the source substance. The available studies do not investigate reproductive and developmental toxic properties and therefore do not allow comparison of the Substance and the source substance in terms of the relevant properties subject to this evaluation.

0.1.3. Conclusion on the read-across approach

18 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.

0.2. Your comments relating to an Assessment of Regulatory Needs document

19 In the comments to the draft decision you also mention that the Substance has undergone an Assessment of Regulatory Needs (ARN) by ECHA and that it concluded that "there was no need for additional risk management measures as the classification in place was a sufficient trigger to insure the protection of workers and the environment".

20 The ARN is not an activity that is directly linked to any regulatory process under REACH or other legislation. In fact, the ARN is part of an activity of "grouping of substances in the chemical universe", that is, a mapping exercise that is mainly based on the information on substances from ECHA's database, and which is designed to help authorities both on European and Member State level to identify possible regulatory needs and prioritise regulatory actions.[2] Every ARN document for this reason contains a disclaimer that the

[2] For more information on the 'Working with Groups' please visit: https://echa.europa.eu/working-with-groups.

conclusions are "without prejudice to any further regulatory work that ECHA, the Member States or other regulatory agencies may initiate at a later stage" and that "[a]ssessment of regulatory needs and their conclusions are compiled on the basis of available information and may change in light of newly available information or further assessment".

21 In any event, ECHA notes that the ARN document in question also proposes compliance check of registrations of the Substance to clarify certain properties of the substance (see page 7-8 of the ARN report of 25 January 2021 for Esters from branched or non-aromatic cyclic dicarboxylic acids and aliphatic alcohols).

22 For all these reasons the ARN cannot be a basis to substantiate an adaptation from the information requirements set out in the REACH Regulation.

Reasons related to the information under Annex VIII of REACH

1. Screening for reproductive/developmental toxicity

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

1.1. Information provided

24 You have adapted this information requirement by using Annex VIII, Section 8.7.1., Column 2. To support the adaptation, you have provided following information:

(i) a reproduction/developmental toxicity screening test (2003) with source substance dimethyl cyclohexane-1,4-dicarboxylate, EC No. 202-347-5

1.2. Assessment of the information provided

25 We have assessed this information and identified the following issue(s):

1.2.1. Read-across adaptation rejected

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

27 Therefore, the information requirement is not fulfilled.

1.3. Specification of the study design

28 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.

29 The study must be conducted with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

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

Reasons related to the information under Annex IX of REACH

2. Pre-natal developmental toxicity study in one species

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

2.1. Information provided

32 You have adapted this information requirement by using a Grouping of substances and read-across approach based on experimental data from the following substances:

i. a prenatal developmental toxicity study (2015) with source substance dimethyl cyclohexane-1,4-dicarboxylate, EC No. 202-347-5.

2.2. Assessment of the information provided

33 We have assessed this information and identified the following issue(s):

2.2.1. Read-across adaptation rejected

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

35 Therefore, the information requirement is not fulfilled.

2.3. Specification of the study design

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

37 The study must be performed with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

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

3. Long-term toxicity testing on aquatic invertebrates

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

3.1. Information provided in the dossier

40 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided the following information:

(i) "In accordance with column 2 of REACH annex IX, further testing on the long-term effects on aquatic organisms does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation."

3.2. Assessment of the information provided in the dossier

41 We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

42 Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

43 Your adaptation is therefore rejected.

3.3. Information provided in the comments to the draft decision

44 In the comment to the draft decision, you disagree to perform the long-term toxicity test on aquatic organisms by invoking the following points:

- you state that the Decision of the Board of Appeal in case A-011-2018 would have changed the interpretation of the Column 2 provision and that this change was only implemented by Commission Regulation (EU) 2022/477[3] applicable from 14 October 2022;
- there is a harmonised classification for the Substance (Aquatic Chronic Category 2, H411);
- that harmonised classification was assessed to be sufficient to ensure the protection of the environment in ECHA's report on "Assessment of regulatory needs" of the "Esters from branched or non-aromatic cyclic dicarboxylic acids and aliphatic alcohols" group (25 January 2021).

3.4. Assessment of the information provided in the comments to the draft decision

3.4.1. The decision of the Board of Appeal in case A-011-2018 has clarified the interpretation of REACH

45 A Decision of the Board of Appeal clarifies the interpretation of the version of the legal text that is already applicable. The Decision of the Board of Appeal in case A-011-2018 has clarified that the provision in Annex IX, Section 9.1, Column 2 concerned further studies, other than the standard information set out in Column 1. It follows from this that this Column 2 provision does not allow registrants to omit submitting information on long term toxicity to aquatic organisms under Column 1. This was also communicated on ECHA's website on 5 August 2020[4], and this interpretation has been consistently followed in ECHA's practice.

46 Notably, this interpretation was confirmed by ECHA's Board of Appeal also in a more recent decision, in case A-010-2019.

47 ECHA points out that the amendments by Commission Regulation (EU) 2022/477 have merely provided textual clarity, for enhanced legal certainty, of the adaptation rule in Annex IX, Section 9.1, Column 2 but did not change the rule related to the need for further studies dependent on the chemical safety assessment in any contradicting way.

[3] Commission Regulation (EU) 2022/477 of 24 March 2022 amending Annexes VI to X to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

[4] https://echa.europa.eu/-/echa-weekly-5-august-2020, see section 'Adaptations to long-term aquatic toxicity testing'

3.4.2. Existing harmonised classification is not a legal basis to adapt the information requirement

48 A registrant may only adapt this information requirement based on the general rules for adaptation set out in Annex XI.

49 You propose to adapt the information requirement on the basis of an existing harmonised classification for the Substance as Aquatic Chronic Category 2, H411. However, your argumentation does not refer to any legal basis for adaptation under Annex XI.

3.4.3. ECHA's reports on "Assessment of regulatory needs" are not a legal basis to adapt the information requirement

50 As explained above, a registrant may only adapt this information requirement based on the general rules for adaptation set out in Annex XI.

51 As further explained in section 0.2., ECHA's reports on "Assessment of regulatory needs" do not constitute a legal basis for adaptation under Annex XI.

52 Conclusion Based on the information provided in your dossier and in your comments to the draft decision, the information requirement is not fulfilled.

4. Long-term toxicity testing on fish

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

4.1. Information provided in the dossier

54 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following information:

(i) "In accordance with column 2 of REACH annex IX, further testing on the long-term effects on aquatic organisms does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation."

4.2. Assessment of the information provided in the dossier

55 We have assessed this information and identified the following issue:

4.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

56 Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

57 Your adaptation is therefore rejected.

4.3. Information provided in the comments to the draft decision

58 In the comment to the draft decision, you disagree to perform the long-term toxicity test on aquatic organisms by invoking the following points:

- you state that the Decision of the Board of Appeal in case A-011-2018 would have changed the interpretation of the Column 2 provision and that this change was only implemented by Commission Regulation (EU) 2022/477 applicable from 14 October 2022;
- there is a harmonised classification for the Substance (Aquatic Chronic Category 2, H411);
- that harmonised classification was assessed to be sufficient to ensure the protection of the environment in ECHA's report on "Assessment of regulatory needs" of the "Esters from branched or non-aromatic cyclic dicarboxylic acids and aliphatic alcohols" group (25 January 2021).

59 You also propose to adapt this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) according to Annex XI, section 1.3 of REACH and submit the following pieces of information:

i. A prediction from model ECOSAR v1.11, with chemical class: "Esters", and model "Fish ChV",

ii. A prediction from model ECOSAR v1.11, with chemical class: "Neutral Organics", and model "Fish ChV",

iii. A prediction from model KREATIS iSafeRat® fishEC10 v1.5, with mode of action "MechoA 2.1" (mono-/poly-esters whose hydrolysis products are narcotics).

4.4. Assessment of the information provided in the comments to the draft decision

4.4.1. The decision of the Board of Appeal in case A-011-2018 has clarified the interpretation of REACH

60 As explained above in section 3.4.1, ECHA consistently applies the interpretation of the rule set out in Annex IX, Section 9.1, Column 2 as clarified by the Board of Appeal.

4.4.2. Existing harmonised classification is not a legal basis to adapt the information requirement

61 As explained above in section 3.4.2, an existing harmonszed classification does not constitute a legal basis for adaptation.

4.4.3. ECHA's reports on "Assessment of regulatory needs" are not a legal basis to adapt the information requirement

62 As explained above in section 3.4.3, ECHA's reports on "Assessment of regulatory needs" do not constitute a legal basis for adaptation.

4.4.4. Source of information (i): ECOSAR v1.11, with chemical class: "Esters", and model "Fish ChV"

63 Under Guidance on IRs and CSA, Section R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. For that purpose, the fourth OECD principle requires that appropriate measures of the internal performance (i.e. goodness-of-fit and robustness) and predictivity of the model are available.

64 To have appropriate robustness, a model must be built from a training set which includes a sufficient number of substances.

65 However, the training set of model "Fish ChV" with chemical class "Esters" in ECOSAR v1.11 is based on only 4 data points.

66 On this basis, the performance and the predictivity of the model is very poor. In your comments to the draft decision, you acknowledge that the model is invalid, and you do not propose to use it for your CSA.

4.4.5. Source of information (ii): ECOSAR v1.11, with chemical class: "Neutral Organics", and model "Fish ChV"

67 Under Guidance on IRs and CSA R.6.1.5.3., a substance must fall within the applicability domain specified by the model developer.

68 The Substance contains two ester groups.

69 As indicated in the helpfile of the model, the applicability of model "Fish ChV" with chemical class "Neutral Organics" in ECOSAR v1.11 is limited to substances belonging to the following classes: alcohols, acetals, ketones, ethers, alkyl halides, aryl halides, aromatic hydrocarbons, halogenated aromatic hydrocarbons, halogenated aliphatic hydrocarbons, sulfides and di-sulfides. Esters are however not mentioned.

70 Moreover, the training set of the model does not cover chemicals with ester functional groups.

71 Therefore, you have not demonstrated that the Substance falls within the applicability domain of that model.

4.4.6. Source of information (iii): KREATIS iSafeRat® fishEC10 v1.5, with mode of action "MechoA 2.1"

72 Under Guidance on IRs and CSA R.6.1.5.3., a prediction is within the applicability domain of the model, when, among others, the Substance falls within the descriptor, structural, mechanistic and metabolic domains.

73 In the documentation of the model (iSafeRat® fishEC10 v1.5 with mode of action "MechoA 2.1") provided with your comments, the applicability domain of the model is defined by:

- Descriptor domain: subcooled liquid water solubility,
- Structural fragment domain: not considered as a relevant domain since the model is based on a mechanistic approach (mechanism of action),
- Mechanistic domain: mono-/poly-esters whose hydrolysis products are narcotics (MechoA 2.1),
- Metabolic domain: not relevant.

74 It is also indicated that the training set of that model contains 6 substances. However, no more details are provided, in particular the chemical identity and descriptor data for the substances in the training set are not presented. You explain that the training set of that model is proprietary and is not available to you.

75 The model documentation indicates that the structural domain is not considered relevant since the model is based on a mechanistic approach. However, ECHA considers that the structural fragment domain is relevant for mechanistic models too, for the reasons detailed below.

76 The toxicity of the Substance may be driven or modified (i.e. either increased or mitigated toxicity) by structural fragments not represented in the training set of the model.

77 Conversely, the toxicity of the substances in the training set may be driven or modified by structural fragments not represented in the Substance.

78 In a publication[5], the developers of the model explain that the mechanism of action for the model ("MechoA 2.1") relies on the following hypothesis:

79 "3 mechanisms occur simultaneously: direct narcotic toxicity of the parent ester, toxicity due to the acidity generated by the hydrolysis of the ester, and the narcotic effect of the hydrolysis products, a carboxylate and an alcohol. As proposed by Jaworska et al.(1995), the toxicity of esters will therefore be related to the rate of uptake of the molecule by the organism and the metabolic rate of hydrolysis of the molecule".

80 However, the toxicity of the Substance and of the substances in the training set may be driven or modified by distinct mechanisms, different than those considered in the model hypothesis.

81 For example, the Substance, the substances in the training set or their respective hydrolysis products may contain structural fragments that may cause different mode of actions, and not only narcotic toxicity.

82 Furthermore, information on the rate of uptake by the organisms and on the metabolic rate of hydrolysis is available neither for the Substance nor for the substances in the training set. The structural characteristics of the substances (e.g. potential steric hindrance, possible molecular conformations or configurations) may influence their uptake and metabolism.

83 You do not have access to the training set of the model. Therefore, you cannot demonstrate that the Substance falls within its applicability domain.

4.5. Conclusion

84 Based on the information provided in your dossier and in your comments to the draft decision, the information requirement is not fulfilled.

4.6. Study design and test specifications

85 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.).

[5] Thomas PC, Bicherel P, Bauer FJ. How in silico and QSAR approaches can increase confidence in environmental hazard and risk assessment. Integr Environ Assess Manag. 2019 Jan;15(1):40-50. doi: 10.1002/ieam.4108. PMID: 30447098.

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).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

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

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

The compliance check was initiated on 17 November 2021.

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

ECHA took into account your comments and did not amend the requests.

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. This also gives you the "*possibility to first run the OECD TG 421/422 study (information request 1) and assess if the results of this study will allow fulfilling the bridge required between the two substances for the reprotoxicity endpoint before running the OECD TG 414 (Information request 2)*", which you raise in your comments to the draft decision.

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

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

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

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

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;

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

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[6].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

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

- the 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 and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

2. General recommendations for conducting and reporting new tests

2.1. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in Guidance on IRs & CSA, Section R.11.4.2.2, you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesize its relevant constituents and/or fractions.

References to Guidance on REACH and other supporting documents can be found in Appendix 1.