~~Confidential~~

Helsinki, 12 June 2023

Addressees
Registrant(s) of JS_70969-58-3 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
29/05/2013

Registered substance subject to this decision ("the Substance")
Substance name: Diisobutyl hexahydrophthalate
EC/List number: 275-069-5

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***21 September 2026***.

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

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

1. Simulation testing on ultimate degradation in surface water also requested below (triggered by Annex VIII, Section 9.2.)

2. Identification of degradation products also requested below (triggered by Annex VIII, Section 9.2.)

3. Bioaccumulation in aquatic species also requested below (triggered by Annex VIII, Sections 9.3, Column 2.)

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

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

5. 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)

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

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

8. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

9. Identification of degradation products (Annex IX, 9.2.3.; using test method: EU C.25./OECD TG 309)

10. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: EU C.13./OECD TG 305, aqueous exposure)

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.

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. In addition, the studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in this Appendix.

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 grouping and read-across approach under Annex XI, Section 1.5:

i. Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)

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

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

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

0.1.1. Predictions for toxicological properties

5 You have not provided a read-across justification document or hypothesis.

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

i. dibutyl phthalate EC No. 201-557-4

7 Although you did not provide reasoning for the prediction of toxicological properties ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects and that you predict the properties of your Substance based on a worst-case approach.

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

0.1.1.1. Absence of read-across documentation

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

10 You have provided robust study summary for study conducted with another substance than the Substance in order to comply with the REACH information requirements. However, you have not provided documentation as to why this information is relevant for the Substance and thus why the properties of the Substance may be predicted from information on the source substance(s).

11 More specifically, you have not used the source substance for predicting any properties for the Substance or explained why the information is included in your registration dossier. You

have conducted hazard assessment for the Substance based on OECD TG 422 study available with the Substance.

12 Your DNEL derivation does not consider the source substance target organ toxicity reported in the source 90-day repeated dose toxicity study.

13 In the absence of such documentation explaining why the information on the source substance has been included in your documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance.

0.1.1.1. Bias of the prediction

14 In order to make an accurate prediction of ecotoxicological and toxicological properties all relevant information must be considered in the prediction. If not all information is considered in the read-across approach, bias can be introduced in the predictions which may result in an over/underestimation in the prediction (RAAF, 2017; Chapter 4.5.1.5.). Bias may be caused by incorrect/incomplete selection of source substance(s); or due to a particular selection of study(ies) performed on the source substance(s).

15 To justify the selection of source substances, you must provide documentation how the source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s), which other substances have been considered and why they have been discarded (RAAF, 2017, Chapter 4.4.1.5 and 4.5.1.5). If there are structural analogue(s) not used as source substances and data show significantly different results for the properties to be predicted without any justification for setting aside these different results, then the proposed prediction are considered biased.

16 You report information from the aromatic source substance dibutyl phthalate (EC 201-557-4). You have not provided any justification on the selection of the source substance used to predict the properties of the Substance.

17 Another analogue substance, cyclohexane-1,4-dicarboxylic acid (EC 214-068-6) share the same chemical cyclohexane di carboxylic acid structure as the Substance with the difference of the esterised carboxylic acid functionalities with the Substance.

18 A 90-day repeated dose toxicity study is provided on cyclohexane-1,4-dicarboxylic acid reported microscopic lesions in the liver and thymus (centrilobular hypertrophy of the hepatocytes and lymphoid depletion in thymus).

19 Cyclohexane-1,4-dicarboxylic acid may be a closer structural analogue of the Substance than the source substance that you have identified because of the shared cyclohexane moiety. The available data on cyclohexane-1,4-dicarboxylic acid indicates significantly different results showing higher concern on target organ toxicity after repeated exposure than the study on the source substance because the source study used for the prediction does not report the hypertrophy of hepatocytes and lymphoid depletion. You have not justified why this source substance has not been considered.

20 Therefore, your predictions are biased and may underestimate the hazards of the Substance.

0.1.2. Conclusion on the read-across approach

21 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 VIII of REACH

1. Simulation testing on ultimate degradation in surface water

22 Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

23 This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (Guidance on IRs and CSA, Section R.11.4.). This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP) if it is not readily biodegradable (i.e. <60/70% degradation in an appropriate OECD 301 or OECD 310 test)
- it is potentially bioaccumulative or very bioaccumulative (B/vB) if it has a high potential to partition to lipid storage (*e.g.* log K_{ow} > 4.5).

1.1. Information provided

24 Your registration dossier provides the following:

- The Substance is not readily biodegradable when non-adapted inoculums are used: 16% and 18% degradation was observed after 28d from two distinct OECD 301B studies; 21% degradation after 28d in a ISO 14593 study; 8% degradation after 28d in a OECD 301D study. As explained under Request 8 of this decision, the other pieces of information you have provided for assessing the biodegradability of the Substance do not modify the conclusion that the Substance is not readily biodegradable. Therefore, it is not possible to rule out that the Substance is persistent or very persistent.
- The Substance has a high potential to partition to lipid storage (log K_{ow} of 4.83, based on OECD TG 117). As explained under Request 10 of this decision, the other pieces of information you have provided for assessing the bioaccumulation of the Substance do not modify the conclusion that the Substance is potentially bioaccumulative or very bioaccumulative.

25 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

26 The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed in Request 8.

2. Identification of degradation products

27 Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

28 Under Annex VIII, Section 9.3., Column 2, further information on bioaccumulation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the bioaccumulation properties of the substance.

29 As already explained in Request 1, the Substance is a potential PBT/vPvB substance.

30 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

31 The examination of the available information or adaptations, as well as further information on the selection of the approach to generate this information are addressed in Request 9.

3. Bioaccumulation in aquatic species

32 Bioaccumulation in aquatic species is required for the purpose of PBT/vPvB assessment (Annex I, Sections 0.6.1 and 4 to REACH).

3.1. Triggering of the information requirement

1 Under Annex VIII, Section 9.3., Column 2, further information on bioaccumulation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the bioaccumulation properties of the substance.

2 Therefore, this information requirement is triggered in case if for example additional information on bioaccumulation as set out in Annex XIII, point 3.2.2, is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1 of that Annex.

33 As already explained in Request 1, the Substance is a potential PBT/vPvB substance.

34 Therefore, the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species.

35 The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed in Request 10.

Reasons related to the information under Annex IX of REACH

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

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

4.1. Information provided

37 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 sub-chronic toxicity study (1995) with the source substance dibutyl phthalate, EC No. 201-557-4

ii. a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (2013) with the Substance.

4.2. Assessment of the information provided

4.2.1. Read-across adaptation rejected

38 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.

4.2.2. Study with the Substance not adequate for the information requirement

39 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:

i. dosing of the Substance daily for a minimum of 90 days

40 In study (ii), the following specifications are not according to the requirements of the OECD TG 408:

i. dosing of the Substance daily for a minimum of 90 days, because the study used daily dosing of the Substance for approximately 42 days.

41 The information provided does not cover the key parameter(s) required by the OECD TG 408.

42 Therefore, the information requirement is not fulfilled.

4.3. Specification of the study design

43 Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance; Guidance on IRs and CSA, Section R.7.5.6.3.2.

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

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

46 In your comments to the draft decision, you noted the request and did not provide comments. Appendix 2 addresses your decision deadline extension request.

5. Pre-natal developmental toxicity study in one species

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

5.1. Information provided

48 You have provided:

i. a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (2013) with the Substance

5.2. Assessment of the information provided

5.2.1. Study not adequate for the information requirement

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

a) at least 20 female animals with implantation sites are included for each test and control group;
b) the foetuses are examined for sex and body weight, external, skeletal and soft tissue alterations (variations and malformations).

50 That study does not cover the key parameters of the OECD TG 414 such as:

a) at least 20 female animals with implantation sites included for each test and control group, as the study provided has 10 female animals in each group
b) foetuses are examined for sex and body weight, external, skeletal and soft tissue alterations (variations and malformations).

51 The study is not adequate for the information requirement and is therefore rejected.

5.3. Specification of the study design

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

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

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

55 In your comments to the draft decision, you noted the request and did not provide comments. Appendix 2 addresses your decision deadline extension request.

6. Long-term toxicity testing on aquatic invertebrates

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

6.1. Information provided in your dossier

57 In your registration dossier you have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs), more specifically ECOSAR v1.00, with chemical class: "Esters", and model "Daphnia ChV".

6.2. Assessment of the information provided in your dossier

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

6.2.1. Inadequate documentation of the model (QMRF)

59 Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF). A QMRF must report, among others, an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

60 The information you have provided in your dossier is insufficient to assess the predictivity of the model as you have not provided the training set and validation statistics.

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

6.2.2. Lack of documentation of the prediction (QPRF)

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

63 The information you have provided in your dossier is insufficient to assess the quality of the prediction. In particular, you have not provided the training set and the validation sets used for this model. Therefore, it is no possible to verify whether the values predicted by the model for analogue substances are consistent with experimental results.

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

6.3. Information provided in your comments

65 In the comments to the draft decision, you do not agree to perform the requested study. You present a new Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) according to Annex XI, section 1.3 of REACH.

66 You have derived a 21-day NOEC for reproduction of Daphnia magna using a trend analysis developed with the OECD QSAR Toolbox v4.4.1.

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

i. the predictions need to be derived from scientifically valid models,

ii. the substance must fall within the applicability domain of the models,

iii. results need to be adequate for the purpose of risk assessment or classification and labelling, and

iv. adequate and reliable documentation of the method must be provided.

68 With regard to these conditions, we have identified the following issues:

6.3.1. Inadequate documentation of the model (QMRF)

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

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

70 In your comments to the draft decision and in the associated documentation, you indicate that a total of 12 data points from 9 different chemicals were used to constitute the training set of your model.

71 However, you have not provided the data, the information on the experimental protocol used to generate those data, or on the data quality for the dataset used to develop the model. In the absence of such documentation, ECHA cannot trace the source and verify the quality of the individual data points. As such, the information provided is insufficient for ECHA to assess the quality and reliability of those data and how they could support the prediction.

6.3.2. The prediction is not adequate due to low reliability

72 Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest,
- reliable input parameters are used,
- the prediction must be reliable based on the representativeness and homogeneity of the elements in the training set.

73 You have selected 9 different substances to constitute the training set of your model by using several profilers included in the OECD QSAR Toolbox:

- US-EPA New Chemical Categories: "Esters (Acute toxicity)"
- Aquatic toxicity classification by ECOSAR: "Esters"
- Organic functional groups, Norbert Haider (checkmol): "Carboxylic acid derivative" and "Carboxylic acid ester"
- Substance type: "Discrete chemical", "Organic", "Mono constituent".
- Chemical elements: "Group 14 - Carbon C" and "Group 16 - Oxygen O"

74 The three first profilers are largely equivalent and overlapping as they select any substances containing an ester group. The two last profilers exclude substances containing any heteroatoms other than oxygen. Therefore, the criteria to constitute the training set of your model are quite unspecific. The training set includes mono-, di-, tri- and tetra-esters, with various carboxylic acid and alcohol moieties, with different chain length, linear or branched. Your Substance is a diester consisting of a non-aromatic cyclic dicarboxylic acid with two C4 aliphatic branched alcohol moieties.

75 The values of the structural similarity indices that you report in your comments show that the substances in the training set are not only very different from the Substance but also generally very different from each other. Therefore, you have not demonstrated that the training set of your model is homogeneous. This significantly affects its representativeness for the Substance you aim to predict.

76 The heterogeneity of the training set increases the uncertainty on the prediction which is partly reflected by the large 95% prediction interval reported by the OECD QSAR Toolbox: i.e. 0.0223 to 7.07 mg/L. This makes the predicted results too uncertain for the purpose of the classification and labelling and/or risk assessment.

77 Therefore, the information provided in your comments does not establish that the training set used for your model is representative and homogeneous. You have not established that your model predicts well substances that are similar to the Substance, and you have not established that it is applicable to your Substance with the necessary level of reliability. Therefore, you have not demonstrated that your model is scientifically valid and that the prediction from this model is adequate for the purpose of classification and labelling and/or risk assessment.

6.4. Conclusion

78 On those bases, the information requirement is not fulfilled.

7. Long-term toxicity testing on fish

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

7.1. Information provided in your dossier

80 In your registration dossier you have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs), more specifically ECOSAR v1.00, with chemical class: “Esters”, and model “Fish ChV”.

7.2. Assessment of the information provided in your dossier

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

82 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 using the learning data set) and predictivity (using a test data set) of the model are available.

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

84 You have not provided measures of the internal performance and predictivity of the model.

85 According to the information you have provided, the training set of the model is based on only 3 data points.

86 You have not provided other information on the training set, in particular the identity and characteristics of the substances included in this training set.

87 You have not explained why this would be sufficient to quantify the performance and the predictivity of the model. However, both can be expected to be very poor considering the very limited number of data points used to develop this model. On this basis and in the absence of measures of the internal performance and predictivity of the model, you have not established the scientific validity of the model.

7.3. Information provided in your comments

88 In the comments to the draft decision, you do not agree to perform the requested study. You present a new Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) according to Annex XI, section 1.3 of REACH.

89 You have derived a long-term NOEC for the mortality of fish using a trend analysis developed with the OECD QSAR Toolbox v4.4.1.

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

v. the predictions need to be derived from scientifically valid models,

vi. the substance must fall within the applicability domain of the models,

vii. results need to be adequate for the purpose of risk assessment or classification and labelling, and

viii. adequate and reliable documentation of the method must be provided.

91 With regard to these conditions, we have identified the following issues:

7.3.1. Inadequate documentation of the model (QMRF)

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

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

93 In your comments to the draft decision and in the associated documentation you have provided as attached files, you indicate that a total of 13 data points from 9 different chemicals were used to constitute the training set of your model.

94 However, you have not provided the data, the information on the experimental protocol used to generate those data, or on the data quality for the dataset used to develop the model. In the absence of such documentation, ECHA cannot trace the source and verify the quality of the individual data points. As such, the information provided is insufficient for

ECHA to assess the quality and reliability of those data and how they could support the prediction.

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

95 Results from (Q)SAR models must be equivalent to results obtained from the required experimental test in order to be adequate for risk assessment or classification and labelling. The corresponding study that must normally be performed for this particular information requirement is the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) (Guidance on IRs and CSA, Section R.7.8.2.), for which the following key parameters must be measured:

- hatching of fertilised eggs and survival of embryos, larvae and juvenile fish, and
- the appearance and behaviour of larvae and juvenile fish, and
- the weight and length of fish at the end of the test.

96 You have provided a result from a (Q)SAR model which is said to predict the mortality of fish.

97 As explained above, there is no information on the experimental protocol(s) used to generate the data in the training set of the model. Therefore, it is not clear whether the mortality predicted by the model refers to embryos, larvae or juvenile fish.

98 Furthermore, the model does not predict the effects on other key parameters of OECD TG 210, such as egg hatch, larval abnormalities, the weight and length of fish at the end of the test.

99 Therefore, the prediction is not equivalent to results obtained from the required experimental test. Therefore, it is not adequate for the purpose of classification and labelling and/or risk assessment.

7.3.3. The prediction is not adequate due to low reliability

100 Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest,
- reliable input parameters are used,
- the prediction must be reliable based on the representativeness and homogeneity of the elements in the training set.

101 You have selected 9 different substances to constitute the training set of your model by using several profilers included in the OECD QSAR Toolbox:

- US-EPA New Chemical Categories: "Esters (Acute toxicity)"
- Aquatic toxicity classification by ECOSAR: "Esters"
- Organic functional groups, Norbert Haider (checkmol): "Carboxylic acid derivative" and "Carboxylic acid ester"
- Substance type: "Discrete chemical", "Organic", "Mono constituent".
- Chemical elements: "Group 14 - Carbon C" and "Group 16 - Oxygen O"

102 The three first profilers are largely equivalent and overlapping as they select any substances with an ester group. The two last profilers exclude substances containing any heteroatoms other than oxygen. Therefore, the criteria to constitute the training set of your model are quite unspecific. The training set includes mono-, di-, tri- and tetra-esters, with various carboxylic acid and alcohol moieties, with different chain length, linear or branched. Your Substance is a diester consisting of a non-aromatic cyclic dicarboxylic acid with two C4 aliphatic branched alcohol moieties.

103 The values of the structural similarity indices that you report in your comments show that the substances in the training set are not only very different from the Substance but also generally very different from each other. Therefore, you have not demonstrated that the training set of your model is homogeneous. This significantly affects its representativeness for the Substance you aim to predict.

104 The heterogeneity of the training set increases the uncertainty on the prediction which is partly reflected by the large 95% prediction interval reported by the OECD QSAR Toolbox: i.e. 0.156 to 32.4 mg/L. This makes the predicted results too uncertain for the purpose of the classification and labelling and/or risk assessment.

105 Therefore, the information provided in your comments does not establish that the training set used for your model is representative and homogeneous. You have not established that your model predicts well substances that are similar to the Substance, and you have not established that it is applicable to your Substance with the necessary level of reliability. Therefore, you have not demonstrated that your model is scientifically valid and that the prediction from this model is adequate for the purpose of classification and labelling and/or risk assessment.

7.4. Conclusion

106 On those bases, the information requirement is not fulfilled.

7.5. Study design and test specifications

107 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.).

8. Simulation testing on ultimate degradation in surface water

108 Simulation testing on ultimate degradation in surface water is an information requirement under Annex IX to REACH (Section 9.2.1.2.).

8.1. Information provided

109 You have adapted this information requirement by invoking Column 2 of Annex IX, Section 9.2.1.2. To support the adaptation, you have provided following information:

110 "In accordance with REACH Regulation 1907/2006/EC (Annex IX - 9.2.1.2 & 9.2.1.4 - column 2) simulation tests of biodegradation in water and sediment do not need to be conducted as the substance is biodegradable".

8.2. Assessment of information provided

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

112 Annex IX, Section 9.2.1.2., Column 2 provides that the study need not be conducted if the Substance is readily biodegradable. The information available to assess the ready biodegradability of the Substance must comply with OECD test guidelines 301 or 310 (Article 13(3) of REACH) or with the general rules for adaptation specified in Annex XI.

113 For assessing the ready biodegradability of the Substance, your registration dossier provides the following 6 pieces of information:

i. A study according to OECD 301B but where an adapted inoculum was used. That study shows 99% degradation of the Substance after 28 days,

ii. A study according to OECD 301B which shows 18% degradation of the Substance after 28 days,

iii. A study according to OECD 301B which shows 16% degradation of the Substance after 28 days, and 21% degradation after 60 days,

iv. A study according to ISO 14593 which shows 21% degradation of the Substance after 28 days, and 23% degradation after 56 days,

v. A study according to OECD 301D which shows 8% degradation of the Substance after 28 days,

vi. A result from the BIOWIN program (version 4.10) which predicts that the Substance is readily biodegradable.

8.2.1. Study (i) is not adequate to assess the ready biodegradability of the Substance

114 OECD TG 301 requires that the inoculum must not be pre-adapted to the test material.

115 However, for study (i), an activated sludge adapted to the Substance was used. The sludge was fed daily with a synthetic sewage during an adaptation period to the substance of 32 days.

116 The conditions applied in study (i) are highly favourable to the selection and/or adaptation of micro-organisms capable of degrading the Substance. Therefore study (i) is not appropriate to assess the ready biodegradability of the Substance.

8.2.2. Studies (ii)-(v) indicate that the Substance is not readily biodegradable

117 All other experimental studies (studies (ii)-(v)) indicate that the Substance is not readily biodegradable, even after a prolonged test duration.

8.2.3. The prediction from BIOWIN (piece of information (vi)) is less reliable than studies (ii)-(v)

118 Guidance on IRs and CSA, Section R.7.9.5.1. explains that QSAR models for predicting ready biodegradation are not yet sufficiently reliable to predict unequivocally rapid degradation. More generally, Guidance on IRs and CSA, Section R.6.1.5.3. specifies that, among others, a QSAR model must predicts well substances that are similar to the substance of interest. By extension, the prediction of a QSAR model must be consistent with valid experimental results obtained for the Substance.

119 The BIOWIN program (piece of information (vi)) predicts that the Substance is readily biodegradable. Valid experimental ready biodegradability studies on the Substance are also available (studies (ii) – (v)), which all show that the Substance is not readily biodegradable. The prediction from the BIOWIN program is not consistent with those experimental results.

120 Therefore, the prediction from the BIOWIN model (piece of information (vi)) is not reliable.

8.3. Conclusion

121 Therefore, the Substance cannot be regarded as readily biodegradable.

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

123 Therefore, your adaption is rejected.

124 In your comments to the draft decision, you noted the request and did not provide comments for this information requirement.

8.4. Study design and test specifications

125 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

126 You must perform the test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (Guidance on IRs and CSA, Section R.11.4.1.1.3.).

127 The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (Guidance on IRs and CSA, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 309.

128 As specified in Guidance on IRs and CSA, Section R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test material concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (Guidance on IRs and CSA, Section R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

129 Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 309; Guidance on IRs and CSA, Section R.11.4.1.).

9. Identification of degradation products

130 Identification of degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

9.1. Assessment of the information provided

131 You have provided no information on the identity of transformation/degradation products for the Substance.

132 Therefore, this information requirement is not met.

133 In your comments to the draft decision, you noted the request and did not provide comments for this information requirement.

9.2. Study design and test specifications

134 Regarding the selection of appropriate and suitable test method(s), the method(s) will have to be substance-specific. Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You may obtain this information from the degradation study requested in Requests 1 and 8.

135 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Requests 1 and 8) must be conducted at 12°C and at a test concentration < 100 µg/L. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, e.g. 20°C) and at higher application rate (i.e. > 100 µg/L).

10. Bioaccumulation in aquatic species

136 Bioaccumulation in aquatic species is an information requirement under Annex IX to REACH (Section 9.3.2.).

10.1. Information provided in your dossier

137 In your registration dossier you have adapted this information requirement by using a weight of evidence approach (Annex XI, section 1.2) based on the following sources of information:

(i) A prediction from QSAR program VEGA, model CAESAR BCF v.1.0.0.11.

(ii) A prediction from QSAR program BCFBAF v.3.01, regression-based model

(iii) A prediction from QSAR model BCFBAF v.3.01, Arnot-Gobas upper trophic model

10.2. Assessment of the information provided in your dossier

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

10.2.1. Your weight of evidence approach is not reliable

139 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.

140 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.

141 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.

142 ECHA has assessed the validity of your adaptation.

143 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 9.3.2. includes similar information that is produced by the OECD TG 305. OECD TG 305 requires the study to investigate the following key elements:

1. the uptake rate constant (k_1) and loss rate constants including the depuration rate constant (k_2), and/or
2. the bioconcentration factor (BCF): steady-state bioconcentration factor (BCF_{SS}), and/or the kinetic bioconcentration factor (BCF_K), and/or
3. the biomagnification factor (BMF).

10.2.1.1. Uptake rate constant (k1) and loss rate constants including the depuration rate constant (k2)

144 The source of information (iii) (BCFBAF v.3.01, Arnot-Gobas upper trophic model) may provide relevant information on uptake rate constant (k_1) and loss rate constants including the depuration rate constant (k_2), not the other two sources of information.

145 However, the reliability of this source of information is significantly affected by the following deficiencies:

146 First, under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with information available for other related endpoint(s).

147 The Arnot-Gobas model implemented in BCFBAF v.3.01 predicts the bioconcentration factor (BCF) and the bioaccumulation factor (BAF) for fish from different trophic levels. The uptake rate constant (k_1) and loss rate constants including the depuration rate constant (k_2) can as well indirectly be estimated from this model. The model assumes that the bioaccumulation and the bioconcentration of a substance in fish can be predicted from the kinetic rate constants for different uptake routes and for different elimination routes. Therefore, the reliability of the model predictions is highly dependent on the reliability of those kinetic rate constants as input parameters.

148 Using allometric models, all the kinetic rate constants implemented in the model, except the metabolic biotransformation rate constant, are estimated from generic assumptions

such as a generic weight or lipid content of the fish and the log Kow of the substance (Appendix K of the helpfile of the BCFBAF v.3.01 program). No information is provided on the goodness-of-fit and predictivity of the allometric models used. Therefore, the reliability of the kinetic rate constants predicted from those allometric models is unknown. Therefore, those kinetic rate constants cannot be regarded as reliable input parameters.

149 The metabolic biotransformation rate constant (k_M) is estimated separately based on the structural fragments present in the substance. Based on the documentation available in the helpfile of the BCFBAF v.3.01 program, predictions for the metabolic biotransformation rate constant from the Arnot-Gobas model can be very inaccurate. Prediction errors of more than 2 orders of magnitude are apparent in the validation set of the model. Furthermore, the molecules in the training set that are most structurally similar[2] to the Substance have experimental values that disagree with their predicted values. Therefore, the model does not predict well the metabolic biotransformation rate constant of substances that are structurally similar to the Substance.

150 Therefore, the predictions of the kinetic rate constants, in particular the uptake rate constant (k_1) and loss rate constants including the depuration rate constant (k_2) are not considered reliable:

- the model does not predict well the metabolic biotransformation rate constant of substances that are structurally similar to the Substance,
- the reliability of the kinetic rate constants determined from allometric models is unknown.

151 Second, Section 2.1. of Annex XIII requires that you must generate 'assessment information' (as described in Section 3.2 of Annex XIII), such as a bioaccumulation study, if the results from screening information (as described in Section 3.1 of Annex XIII) indicate that the Substance may have PBT or vPvB properties. Section 2.1. of Annex XIII further specifies that assessment information does not have to be generated for the purpose of the PBT/vPvB assessment only if screening information does not indicate potential P or B properties.

152 Therefore, as long as a piece of screening information indicates that the Substance could potentially be persistent (P) and bioaccumulative (B), then assessment information needs to be generated.

153 For the B/vB assessment, results from a bioconcentration or bioaccumulation study in aquatic species constitutes assessment information for B or vB properties (Section 3.2.2. of Annex XIII of REACH). However, QSAR predictions are not mentioned as possible assessment information for the PBT/vPvB assessment. (Q)SAR models may however be used, but only together with other information in a Weight-of-Evidence approach (see ECHA Guidance R.11, Section R.11.4.1.2.10).

154 As already explained in Request 1, the Substance is a potential PBT/vPvB substance.

155 The BCF values you have reported are all from QSAR predictions. They are regarded as 'screening information' (Section 3.1, Annex XIII of REACH), not as 'assessment information' (Section 3.2, Annex XIII of REACH) as it is based on a QSAR prediction.

156 Therefore, the provided study cannot be considered a reliable source of information that could contribute to the conclusion on this key parameter investigated by the required study.

[2] The structural similarity was assessed using different methods. A measure of structural similarity between different molecules can be obtained by calculating similarity indices (e.g. Tanimoto/Jaccard, Dice/Hodgkin, Cosine/Carbo) between "fingerprints" of the molecules. Common examples of methods for calculating molecular fingerprints are included in the freely available Chemistry Development Kit (CDK): CDK Standard, CDK Extended, CDK PubChem, CDK FCFP6, CDK ECFP4, CDK MACCS.

10.2.1.2. Bioconcentration factor (BCF)

157 The three sources of information (i), (ii) and (iii) may provide relevant information on bioconcentration factors (BCF).

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

159 First, under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with information available for other related endpoint(s).

i. Model CAESAR BCF v.1.0.0.11. included in program VEGA predicts a BCF value of 22 for the Substance. The molecules in the training set that are most structurally similar[3] to the Substance have experimental values that disagree with the predicted values. Version 1.0.0.11. of the CAESAR BCF model is obsolete. More recent versions of the program predict the same BCF value of 22 for the Substance, but also indicates explicitly that this prediction is not reliable for the following reasons:

> - "*The accuracy of prediction for similar molecules found in the training set is not adequate*";
>
> "*Similar molecules found in the training set have experimental values that disagree with the predicted value*";
>
> "*The maximum error in prediction of similar molecules found in the training set has a high value, considering the experimental variability*".

ii. The "regression-based model" included in BCFBAF v.3.01, predicts a BCF value of 714 for the Substance, using a log Kow value of 4.83 as input parameter. However, for that model as well, the molecules in the training set that are most structurally similar[4] to the Substance have experimental values that disagree with the predicted values. The training set of the model is available from the helpfile of the programme, and it is possible to calculate the tolerance interval for this prediction. The uncertainties of a model prediction are due in part to the limited size of the training set (the sampling error) but also to the intrinsic variability of the data. Both aspects can be quantified with a tolerance interval. The upper bound of the 95% tolerance interval (1-sided, significance level: 5%) calculated for a BCF predicted by that model and for a log Kow of 4.83 is >6700. More specifically, based on this model, it can be calculated that the probability that the BCF is above 2000 for a substance with a log Kow of 4.83 is approximately 25% with 95% confidence. Similarly, the probability (with 95% confidence) that the BCF is above 5000 can be calculated as approximately 8%. Therefore, you have not demonstrated that the BCF value predicted for the Substance

[3] The structural similarity was assessed using different methods (different fingerprints and different similarity indices). Recent versions of the CAESAR BCF model also provide a measure of similarity between the predicted molecule and the molecules in the training set.
[4] The structural similarity was assessed using different methods (different fingerprints and different similarity indices).

by the "regression-based model" in BCFBAF v.3.01 is reliable.

iii. The Arnot-Gobas model implemented in BCFBAF v.3.01 predicts a BCF value of 24.68 for the upper trophic level and for the Substance, using a log Kow value of 4.83 as input parameter, and assuming a biotransformation rate constant of 12.22 d^{-1} (normalised to 10 g fish at 15°C). As explained above, this model assumes that the bioaccumulation and the bioconcentration of a substance in fish can be predicted from the kinetic rate constants for different uptake routes and for different elimination routes. Therefore, the reliability of the BCF values predicted by the model is highly dependent on the reliability of those kinetic rate constants. As explained above, the predictions for the kinetic rate constants, and in particular for the biotransformation rate constant, are not reliable. By comparison, assuming that no biotransformation takes place, the model predicts a BCF value of 5832 for the upper trophic level and for a log Kow value of 4.83. Therefore, the BCF values predicted for the Substance by the Arnot-Gobas model are not reliable because the reliability of the input parameters is not established.

160 Therefore, the predictions of the bioconcentration factor (BCF) are not considered reliable from any of the sources of information you have provided.

161 Second, these QSARs do not qualify as assessment information for the purpose of PBT assessment, for the reasons described above.

162 Therefore, the provided studies cannot be considered reliable sources of information that could contribute to the conclusion on this key parameter investigated by the required study.

10.2.1.3. Biomagnification factor (BMF)

163 None of the three sources of information (i), (ii) and (iii) provide directly relevant information on biomagnification factors (BMF).

10.2.1.4. Information provided in your comments

164 In the comments to the draft decision, you do not agree to perform the requested study.

165 You provide further justification for your weight of evidence adaptation:

i. While you acknowledge that the three QSAR models used for you weight of evidence approach have reliability issues, you also argue that they constitute three different and independent sources of information that all consistently predict BCF values below 2000 for the Substance.

ii. Additionally, you explain that the Substance contains two ester groups. You claim that those ester groups are sterically "slightly but not strongly" hindered. On this basis, you assume that its metabolization is plausible. You also refer to available toxicology studies in rats with the Substance or with an analogue. Based on the absence of toxicity following the oral administration of a single dose of the Substance to rats, you conclude that the Substance is either not readily absorbed via the oral route, or that it undergoes extensive first-pass metabolism. Based on toxicokinetics and metabolism studies with an analogue (1,2-Cyclohexanedicarboxylic acid, 1,2-diisononyl ester) you conclude that absorption of the Substance via the oral route is probably limited.

iii. You consider that, taking into account all the available pieces of information, there is sufficient evidence to conclude with a high level of confidence that the Substance has no potential for bioaccumulation. You consider that the uncertainty on that conclusion is very small.

166 However, ECHA notes that:

i. The training sets for the three models are largely overlapping. The training set for the regression-based model and the Arnot-Gobas models in BCFBAF are identical. There is a large overlap between the training sets for model CAESAR BCF in VEGA and the models in BCFBAF: 216 substances are common to both the training set for the CAESAR BCF model (training set of 378 substances) and the training set for the BCFBAF models (training set of 466 substances). Therefore, the three models cannot be regarded as independent sources of information. This diminishes the weight that could normally be given to totally independent sources of information.

ii. No conclusive information is available to claim that metabolization occurs in fish. The available information from the toxicology studies is only relevant for rats and for the oral route. Fish are exposed via water, with a potential uptake of the Substance mainly from the gills, which could potentially lead to a systemic exposure, without first-pass metabolism. Besides, metabolism of the ester groups in the Substance is not demonstrated, due to the unresolved extent of the steric hindrance.

iii. As explained above, all the three QSAR predictions are highly uncertain. Taking this uncertainty into account, it is not possible to rule out that BCF exceeds 2000. Available information on rats does not rule out either that bioaccumulation could occur in fish.

10.2.1.5. Conclusion on the weight of evidence

167 In summary, the sources of information (i) to (iii) provide information on some key parameters: the uptake and depuration rate constants, or the bioconcentration factor (BCF). However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for bioaccumulation in aquatic species.

168 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for bioaccumulation in aquatic species. Therefore, your adaptation is rejected, and the information requirement is not fulfilled.

10.3. Study design and test specifications

169 Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (Guidance on IRs and CSA, Section R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test material in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

170 This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

171 You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

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 request(s) and extended the deadline.

In your comments, you requested an extension of the deadline. The deadline of the decision was 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 should also address the sequential testing where needed.

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: 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[5].

(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[6].

2. General recommendations for conducting and reporting new tests

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

2.1. Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

You are advised to consult Guidance on IRs & CSA, Sections R.7.9, R.7.10 and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. You must revise your PBT assessment when the new information is available.