~~Confidential~~

Helsinki, 23 January 2024

**Addressees**
Registrants of JS_DMDEE as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**
07/09/2017

**Registered substance subject to this decision ("the Substance")**
Substance name: 2,2'-dimorpholinyldiethyl ether
EC number/List number: 229-194-7

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

## DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***30 April 2027***.

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

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

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

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

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

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

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

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

6. 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.

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

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

8. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rat)

The reasons for the request(s) are explained in Appendix 1.

**Information required depends on your tonnage band**

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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

**How to comply with your information requirements**

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

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

**Appeal**

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

**Failure to comply**

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

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

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

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

## Appendix 1: Reasons for the request(s)

**Contents**

**Reasons common to several requests**

*0.1. Read-across adaptation rejected*

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

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study in a second species (Annex IX, Section 8.7.2., column 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):

- morpholine, EC 203-815-1
- and its salt morpholine hydrochloride, EC 233-029-4

7 You provide the following reasoning for the prediction of toxicological properties: "The backbone of both substances is the morpholine group which contains [redacted]. Besides morpholine, the other substance contains two Nethylmorpholine groups coupled by an aliphatic ether bound (2,2'-dimorpholinyldiethyl ether; hereafter named DMDEE). Based on its chemical similarity, comparable properties are expected for morpholine and DMDEE ether in both human and the environment. Also, DMDEE can be structurally comparable, although the molecule is significantly larger and contains an aliphatic ether bound in addition. The ether bound is chemically inert, but might be degraded under environmental or physiological conditions".

8 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance(s).

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

*0.1.1.1. Read-across hypothesis contradicted by existing data*

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 must strengthen the rationale for the read-

across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

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

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

13 However, the results of the information on reproductive and developmental toxicity obtained with the source substance(s) and available on ECHA's dissemination website vary.

14 First, in an extended-one generation study (EOGRTS, OECD TG 443, 2021) performed with morpholine hydrochloride (EC 233-029-4), an increased incidence of F0 and F1 male rats showing dose-dependent tubular degeneration in the testis and subsequent alteration of sperm was observed at 200 mg/kg bw/day and above. In addition, in a prenatal developmental toxicity study (OECD TG 414, 2021), morpholine hydrochloride (EC 233-029-4) induced a higher incidence of aortic arch atresia and skeletal variations in rabbit fetuses at the high-dose level of 210 mg/kg bw/day. Based on these results, a self-classification as Repr. 2 H361fd was applied to this analogue substance. This contrasts with your prediction of absence of developmental effects and non-classification for the Substance.

15 Second, in a sub-acute toxicity study (OECD TG 407, 1994) performed with the Substance, animals in the top dose of 600 mg/kg bw/d had to be killed in extremis due to severe suffering induced by the substance treatment. In the EOGRT study (OECD TG 443, 2021) performed with the source substance morpholine hydrochloride (EC 233-029-4), such extreme effects were not seen at the same top-dose level of 600 mg/kg bw/d, although the exposure duration was far longer than the 28 days of the sub-acute study with the Substance. This contrasts with your prediction of absence of repeated dose toxcicity effects and developmental effects.

16 The available set of data indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the Substance and source substances cause the same type of effect(s).

*0.1.1.2. Missing supporting information to compare the properties of the substances (developmental toxicity)*

17 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). Supporting information must include bridging studies to compare properties of the source substances.

18 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar source substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the target and source substances is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration with the Substance and the source substance(s).

19 For the source substance, you provide the study used in the prediction in the registration dossier. For the Substance, you provide a combined repeated-dose and screening for reproductive/developmental toxicity study from 2013 (OECD TG 422).

20 OECD TG 422 requires that the highest dose level aims to induce toxicity or aims to reach the limit dose.

21 The provided OECD TG 422 study with the Substance tests up to 300 mg/kg bw/d and does not report adverse (reproductive/ developmental toxicity) effects up to this dose nor a justification for such dose.

22 Therefore, the study is unreliable for the purpose of comparing effects seen with source substance(s) and for classifying and labelling on this basis.

23 Thus the data set reported in the technical dossier does not include relevant, reliable and adequate information for the source substance(s) to support your read-across hypothesis for developmental effects.

24 In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar developmental toxicity properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

#### *0.1.1.3. Missing robust study summaries (developmental toxicity)*

25 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 robust study summary for each source study used in the adaptation.

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

27 In your justification document, you have identified the source study prenatal developmental toxicity study in a second species with the analogue substance morpholine. You indicate that that study is "planned to be performed in 2017-2018" but you did not provide any robust study summary for it.

28 You have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the studies. Therefore, you have failed to provide a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.5.

#### *0.1.1.4. Inadequate or unreliable source studies*

29 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

(1) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;
(2) cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

30 Specific reasons why the studies on the source substance(s) do not meet these criteria are explained further below under the applicable information requirement sections 2 and 8. Therefore, no reliable predictions can be made for these information requirements.

### *0.1.2. Conclusion on the read-across approach*

31 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. Column 2 adaptation rejected*

32 You have adapted the following standard information requirements:

- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

#### *0.2.1. Information provided*

33 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. the Substance is not hazardous under Regulation (EC) No 1272/2008 (CLP);

ii. the Substance is not PBT/vPvB

#### *0.2.2. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the studies*

34 Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to aquatic invertebrates, referred to under Column 1, Section 9.1.5. and information on long-term toxicity to fish, referred to under Column 1, Section 9.1.6.

35 Therefore, your adaptation is rejected and the information requirement is not fulfilled.

**Reasons related to the information under Annex VIII of REACH**

## 1. Adsorption/ desorption screening

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

### *1.1. Information provided*

37 In the registration dossier, you have provided an adaptation for this information requirement by using Column 2 of Annex VIII, Section 9.3.1. To support the adaptation, you have provided following information:

i. a claim that on the basis of the Substance's physico-chemical properties, it is expected to have a low potential for adsorption;

ii. a QSAR prediction of log $K_{oc}$ with the Substance.

38 To document your QSAR prediction, you have reported the following pieces of information:

i. a reference to the publication in which the QSAR model is described;

ii. the input parameters that were used.

39 In the comments to the draft decision, you agree that there is a data gap for Annex VIII, Section 9.3.1. Further, you reiterate your intention to adapt the information requirement under Annex XI, Section 1.3 ((Q)SAR).

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

### *1.2. Assessment of the information provided*

#### *1.2.1. Lack of documentation of the model (QMRF)*

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

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

42 Except for a reference to the publication in which the QSAR model is described, you have not provided information about the model.

43 Providing a reference to the publication in which the QSAR model is described is not sufficient, as the registration dossier must include a self-standing documentation of the adaptation used for meeting the information requirement, including the QMRF of the model used.

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

*1.2.2. Inadequate documentation of the prediction (QPRF)*

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

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

46 You provided the following information about the prediction:

i. a reference to the publication in which the QSAR model is described;

ii. the input parameters that were used: the statement that Substance is a base; the log $K_{ow}$ value of the uncharged form of the Substance; the $pK_a$ value of the Substance.

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

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

48 In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement. In particular, ECHA cannot verify the reliability of the prediction for the Substance because it is not supported by the documentation included in the dossier that the Substance falls within the applicability domain of the model and that the model is producing reliable predictions for substances that are structurally similar to the Substance.

49 Based on the above, your adaptation is rejected.

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

51 ECHA acknowledges your intention to improve the documentation of the QSAR prediction for the adsorption/desorption screening information requirement. As indicated in your comments, this strategy relies on data which is yet to be submitted, therefore no conclusion on the compliance can currently be made.

*1.3. Specification of the test selection and study design*

52 The OECD TG 106 Batch Equilibrium Method is the appropriate method to study the adsorption of the Substance. This method uses a range of actual soils and so represents a more realistic scenario than the HPLC (OECD 121) method. The ionisable properties of the Substance should be considered when selecting the appropriate test design. For ionisable substances, soil types should cover a wide range of pH values.

**Reasons related to the information under Annex IX of REACH**

## 2. Sub-chronic toxicity study (90-day)

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

### *2.1. Information provided*

54 You have provided:

(i) a key combined repeated dose and reproduction / developmental screening study through in rats the oral route (OECD TG 422, 2013) with the Substance;

(ii) a supporting subacute repeated dose toxicity study in rats through the oral route (OECD TG 407 study, 1994) with the Substance.

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

(iii) a chronic toxicity study in rats through inhalation (OECD TG 452, 1983) with the analogue substance morpholine (EC 203-815-1).

### *2.2. Assessment of the information provided*

#### *2.2.1. Studies not adequate for the information requirement*

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

a) the exposure duration is at least 90 days;

b) the highest dose level should aim to induce toxicity or reach the limit dose.

57 Studies (i) and (ii) are described as subacute toxicity studies.

a) In study (i) and (ii), the exposure duration was only 36-54 and 28 days, respectively;

b) Study (i) tests up to 300 mg/kg bw/d, which is lower than the limit dose of 1000 mg/kg bw/d, and does not report adverse (reproductive/ developmental toxicity) effects up to this dose. No justification was provided for using such dose.

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

#### *2.2.2. Read-across adaptation rejected*

59 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.

60 Therefore, study (iii) cannot be used to adapt this information requirement.

61 Therefore, the information requirement is not fulfilled.

### *2.3. Specification of the study design*

62 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance, as it is a liquid of low vapour pressure (66 Pa).

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

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

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

## 3. Pre-natal developmental toxicity study in one species

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

### *3.1. Information provided*

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

(i) a pre-natal developmental toxicity study in rats (OECD TG 414, 2009) with the source substance morpholine hydrochloride (EC 233-029-4).

### *3.2. Assessment of the information provided*

#### *3.2.1. Read-across adaptation rejected*

68 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.

69 Therefore, the information requirement is not fulfilled.

### *3.3. Specification of the study design*

70 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species. Publicly available data (OECD TG 414 in rats, 2009; OECD TG 414 in rabbits, 2020) indicates that an analogue substance (morpholine hydrochloride, EC 233-029-4) tests with higher sensitivity in rabbits.

71 As described in section 0.1 of this decision, one of the reasons to reject your read-across adaptation is the fact that you did not take into account all available data on the source substance(s), including the above OECD TG 414 study in rabbits showing developmental toxicity effects, which were not observed in an OECD TG 414 study in rats.

72 Although your read-across adaptation is rejected, morpholine and its neutral salt morpholine hydrochloride remain analogue substances of the Substance and it cannot be excluded that developmental effects are driven by the common morpholine moieties between the Substance and the source susbtances.

73 Based on the Introductory paragraph to Annex IX (and the consideration on the information provided for the second species under request 8 below), it is then appropriate to test in rabbit, as testing first in rat may miss or underestimate toxicity.

74 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1).

75 Therefore, the study must be conducted in rabbits with oral administration of the Substance.

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

## 4. Long-term toxicity testing on aquatic invertebrates

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

### *4.1. Information provided*

78 In the registration dossier, you have provided an adaptation for this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided information on the hazard classification of the Substance and the conclusion of your PBT assessment

79 In the comments to the draft decision, you agree that there is a data gap for Annex IX, Section 9.1.5. Further, you indicate your intention to adapt the information requirement under Annex XI, Section 1.3 ((Q)SAR).

### *4.2. Assessment of the information provided*

80 As explained in Section 0.2., your adaptation is rejected.

81 Therefore, the information requirement is not fulfilled.

82 ECHA acknowledges your intention to provide a QSAR prediction for the long-term toxicity testing on aquatic invertebrates information requirement. As indicated in your comments, this strategy relies on data which is yet to be submitted, therefore no conclusion on the compliance can currently be made.

### *4.3. Study design and test specifications*

83 The Substance is difficult to test due to being ionisable within the environmentally relevant pH range of 4-9 ($pK_a$: 6.8). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

## 5. Long-term toxicity testing on fish

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

### *5.1. Information provided*

85 In the registration dossier, you have provided an adaptation for this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided information on the hazard classification of the Substance and the conclusion of your PBT assessment.

86 In the comments to the draft decision, you agree that there is a data gap for Annex IX, Section 9.1.6.

87 You provide a new adaptation that you consider to be based on Annex XI, Section 3 (Substance-tailored Exposure-driven testing). You provide the following justification:

- "*testing in accordance with Section 8.7 of Annex VIII and in accordance with Annex IX and Annex X may be omitted, based on the exposure scenarios(s) developed in the Chemical Safety Report. In accordance with Annex XI Section 3, it is demonstrated in chapters 9 and 10 of the Chemical Safety Report that the exposure levels estimated in all relevant manufacture and use scenarios do not exceed the appropriate PNEC, and the likelihood and severity of an event occurring due to the physicochemical properties of the substance in the aquatic environment are negligible. Specifically, the risk characterization ratios are <1 for all compartments and there are no physicochemical hazards identified for this substance in the aquatic environment*."

88 On this basis, ECHA understands that you have sought to adapt this standard information requirement under Annex XI, Section 3(2)(a) (substance-tailored exposure-driven testing).

89 Further, ECHA also understands that you reiterate your intention to waive the information requirement on the basis of the Substance's chemical safety assessment according to Annex I.

### *5.2. Assessment of the information provided*

#### *5.2.1. Column 2 adaptation rejected*

90 As explained in Section 0.2., your adaptation provided in the registration dossier is rejected. For the same reasons, your intention to waive the information requirement on the basis of the Substance's chemical safety assessment according to Annex I as set out in your comments is rejected. Furthermore, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

#### *5.2.2. Assessment of the new adaptation provided in your comments*

91 Additionally, we have assessed the new adaptation in your comments to the draft decision, that you consider to be based on Annex XI, Section 3 (Substance-tailored Exposure-driven testing). As explained above, ECHA understands that you have sought to adapt this standard information requirement under Annex XI, Section 3(2)(a) (substance-tailored exposure-driven testing).

92 A substance-tailored exposure-driven testing adaptation must fulfil the cumulative conditions set out under Annex XI, Sections 3(1) as well as 3(2)(a), (b), or (c).

##### *5.2.2.1. Exposure always well below PNEC not demonstrated*

93 The results of the exposure assessment must show that exposures are always well below the PNEC, i.e. RCRs must always be well below 1. This means that a high level of confidence is needed to demonstrate that every RCR is low enough to ensure that the risks are always controlled, under every plausible condition of the manufacture and all identified uses of the Substance. For this purpose, the possible sources of variability and uncertainty must be considered in the assessment of exposure (Guidance on IRs and CSA Chapter R.16, page 68).

94 Uncertainty must be taken into account, either by carrying out the environmental exposure assessment using conservative assumptions and default values, which are provided in Guidance on IRs and CSA Chapters R.16. (Guidance on IRs and CSA Chapter R.19).

95 Alternatively, when the environmental exposure assessment is not based on these generic assumptions, a stepwise, tiered approach including an uncertainty analysis must be conducted. This analysis can be qualitative, deterministic, or probabilistic, to demonstrate that the risk is adequately controlled (Guidance on IRs and CSA Chapter R.19 provides a framework for carrying out a stepwise, tiered approach to uncertainty analysis). The results must be provided in the dossier to demonstrate that the application of such tiered uncertainty analysis gives a clear indication that the risk is adequately controlled (e.g. an increased belief that the (distribution of the) RCR is less than 1).

96 You have provided an exposure assessment reporting 13 exposure scenarios (ES) with quantitative exposure assessment and risk characterisation for each of them.

97 Most exposure assessments are not based on the generic assumptions recommended in Guidance on IRs and CSA Chapter R.16, but you have used less conservative input parameters, in particular for the release factors.

98 You have not provided results of the uncertainty analysis for the environmental exposure assessment ensuring a high level of confidence that the risk is always adequately controlled.

99 Therefore, you have not demonstrated that your exposure assessment is always conservative enough and the RCRs always low enough to cover the possible sources of variability and uncertainty. Thus, exposures cannot be regarded as being always well below the PNEC.

#### *5.2.2.2. Conclusion on the substance-tailored exposure driven testing adaptation*

100 Based on the above, your substance-tailored exposure driven testing adaptation under Annex XI, Section 3 is rejected.

101 Therefore, the information requirement is not fulfilled.

### *5.3. Study design and test specifications*

102 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.).

103 OECD TG 210 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in "Study design and test specifications" under Request 4.

## 6. Simulation testing on ultimate degradation in surface water

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

### *6.1. Information provided*

105 In the registration dossier, you have provided an adaptation for this information requirement and provided the following justification:

(i) "*From available biodegradation tests it was concluded that the substance is not biodegradable under test conditions. No further simulation testing is deemed necessary as it is not expected to improve the current conclusion on biodegradation*."

(ii) In section 2.3. of your dossier (PBT assessment), you conclude that the Substance fulfils the screening criteria for persistence because it is not readily biodegradable, and it is hydrolytically stable.

106 In the comments to the draft decision, you agree that there is a data gap for Annex IX, Section 9.2.1.2. Further, you provide a new adaptation for the information requirement under Annex XI, Section 1.3 ((Q)SAR).

107 We have assessed this information and identified the following issue.

### *6.2. Assessment of information provided in the registration dossier*

#### *6.2.1. Your justification to omit the study has no legal basis*

108 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex IX, Section 9.2.1.2., Column 2.

109 Your justification that you have provided in the registration dossier to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex IX, Section 9.2.1.2., Column 2.

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

111 Therefore, the information requirement is not fulfilled.

112 Additionally, in your comments to the draft decision, you provide a new adaptation of the the information requirement by means of qualitative or quantitative structure-activity relationship models ((Q)SARs), under Section 1.3 of Annex XI. We have assessed this information and identified the following issue.

#### *6.2.2. Assessment of the adaptation provided in your comments*

##### *6.2.2.1. The QSAR result is not equivalent to results obtained from the required experimental test*

113 Results from (Q)SAR models are adequate for risk assessment or classification and labelling when they are equivalent to results obtained from the required experimental test. The corresponding study that must normally be performed for this particular information requirement is OECD TG 309, which measures the following key parameters:

- the rate of aerobic transformation of the test material in natural surface water;
- the identity and rates of formation and decline of transformation/degradation products are determined if those are detected at ≥ 10% of the applied radioactivity (AR) in the total water-sediment system at any sampling time, or are continuously increasing during the study even if their concentrations are <10% AR (unless appropriate justification is provided).

114 You have provided the prediction from a (Q)SAR model CATALOGIC 301C v.12.17, which is an expert system that predicts biological oxygen demand (BOD) and produces concomitant model predictions: primary half-life, ultimate half-life, metabolites and their quantitative distribution. The system is trained on data derived from tests conducted according to the OECD 301C modified MITI I test experimental protocol. Additionally, the system uses a rule based simulator to account for the metabolic logic of microbial catabolism. This simulator is used for predicting the consumption of oxygen and quantities of metabolites. The prediction of primary and ultimate half-lives assumes that biodegradation process follows first order kinetic.

115 The model predicts primary half-life but does not provide a relevant prediction for the rate of aerobic transformation of the test material in natural surface water and the rates of formation and decline of transformation/degradation products. This is because the model is trained on OECD 301C test data and it is using the assumption that biodegradation process follows first order kinetic. The test conditions of the OECD 301C (100 mg/L test material concentration) are expected to result in different degradation kinetics compared to the kinetics observed in an OECD 309 test (where the test material concentration is low enough to reflect those expected in the environment). Therefore, the prediction is not adequate to meet the information requirement for simulation testing on ultimate degradation in surface water for the purpose of classification and labelling and/or risk assessment.

*6.3. Study design and test specifications*

116 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.

117 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.).

118 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.

119 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. Paragraph 52 of the OECD TG 309 provides that the "total recovery (mass balance) at the end of the experiment should be between 90% and 110% for radiolabelled substances, whereas the initial recovery at the beginning of the experiment should be between 70% and 110% for non-labelled substances". NERs contribute towards the total recovery. Therefore, the quantity of the (total) NERs must be accounted for the total recovery (mass balance), when relevant, to achieve the objectives of the OECD TG 309 to derive degradation rate and half-life. The reporting of results must include a scientific justification of the used extraction procedures and solvents.

120 For the persistence assessment by default, total NERs is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NERs may be differentiated and quantified as irreversibly bound or as degraded to biogenic NERs, 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 (NER - summary 2019 (europa.eu)).

121 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.).

## 7. Identification of degradation products

122 Identification of abiotic and biotic degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

### *7.1. Information provided*

123 In the registration dossier, you have provided no information on the identity of transformation/degradation products for the Substance.

124 Therefore, this information requirement is not met.

125 In the comments to the draft decision, you agree that there is a data gap for Annex IX, Section 9.2.3. Further, you provide the following new adaptation for the information requirement under Annex XI, Section 1.3 ((Q)SAR):

- Data generated with the metabolism simulator of OASIS Catalogic v.5.15.2. (model: CATALOGIC 301C, v.12.17), for identifying the potential degradation products of the Substance, and for predicting their respective quantities;
- Data generated with the same software, for screening the PBT/vPvB properties of the potential degradation products that were predicted by OASIS Catalogic.

126 On the basis of the above screening information, you conclude that none of the potential degradation products of the Substance have PBT/vPvB properties.

127 ECHA acknowledges the screening information you have submitted in the comments to the draft decision.

128 We have assessed this information and identified the following issue.

### *7.2. Assessment of information provided*

#### *7.2.1. (Q)SAR adaptation rejected*

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

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

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

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

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

*7.2.1.1. The QSAR result is not adequate for the purpose of classification and labelling and/or risk assessment*

130 The third indent of Annex XI, Section 1.3 specifies that results of (Q)SARs may be used instead of testing when they are adequate for the purpose of classification and labelling and/or risk assessment.

131 Further, Section R.7.9.3.1 of ECHA Guidance on IRs and CSA, Chapter R.7b explains that the suitability of qualitative data on biodegradation pathways may only contribute to the hazard, persistence, and risk assessments as part of a Weight of Evidence approach, if other data are available.

132 In the comments to the draft decision, you have provided screening information on the identity of the potential degradation products from the metabolic transformation map of the Substance, using OASIS Catalogic.

133 Further, you have screened the PBT/vPvB properties of the potential degradation products. For this screening, you have used the same software. Further, you have used the set of potential degradation products, that were predicted by OASIS Catalogic, as an input. You have provided predictions for Log Kow and BOD (Biological Oxygen Demand) of the potential degradation products.

134 Predictions produced by the rule based simulator of CATALOGIC are based on expert knowledge of the possible abiotic and biotic molecular transformations. The potential degradation products are identified on the basis of a library of plausible catabolic reactions. As this library collates known biodegradation pathways that have been published in the open literature and were observed under a range of different experimental conditions (including tests using pure cultures of microorganisms, tests using pre-adapted inocula, etc.), it cannot be excluded that the software identifies a different (e.g., more diverse) set of degradation products compared to the set of degradation products that can, in practice, be experimentally identified under the defined test conditions of simulation tests.

135 Because of this, in the absence of further justification or other type of available data, you have not demonstrated that the set of potential degradation products predicted by OASIS Catalogic represents a prediction result that is sufficient (e.g. not overly conservative) for the hazard, persistence, and risk assessments as the only piece of the information available. On this basis, in itself, your prediction is not sufficiently adequate, for the purposes of classification and labelling and/or risk assessment, or for the purposes of further regulatory risk management (e.g. SVHC identification in cases where PBT/vPvB and/or PMT/vPvM degradation products are identified).

136 Therefore, the information requirement is not fulfilled, and an identification of degradation products is needed.

*7.3. Study design and test specifications*

137 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.

138 Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported. In addition, identified transformation/degradation products must be considered in the CSA including PBT assessment.

139 You must obtain this information from the degradation study requested in Request 6.

140 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Request 6) 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).

**Reasons related to the information under Annex X of REACH**

## 8. Pre-natal developmental toxicity study in a second species

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

### *8.1. Information provided*

142 You have provided the following information on the Substance:

(i) a combined repeated dose and reproduction / developmental screening study through in rats the oral route (OECD TG 422, 2013) with the Substance.

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

(ii) a pre-natal developmental toxicity study in rats (OECD TG 414, 2009) with the source substance morpholine hydrochloride (EC 233-029-4);

(iii) a prenatal developmental toxicity study in a second species (rabbits) planned to be performed in 2017-2018 with the source substance morpholine (EC 203-815-1).

144 In the comments to the draft decision, you indicate your intention to use the requested 90-day repeated dose toxicity study in rats (request 2 of this decision) to inform on the dose-level setting for the pre-natal developmental study in rats and to use the requested pre-natal developmental study in rabbits (request 3 of this decision) to adapt this information requirement. You further argue that these studies should be conducted first, based on animal welfare considerations.

### *8.2. Assessment of the information provided*

#### *8.2.1. Study not adequate for the information requirement*

145 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 to ensure a statistical power equivalent to OECD TG 414;
b) the foetuses are examined for sex and body weight; external, skeletal and soft tissue alterations (variations and malformations); number of resorptions and/or live foetuses; measurement of anogenital distance in live rodent foetuses.

146 Study (i) has been conducted using the OECD TG 422, which is a screening test rather than a conclusive developmental toxicity study.

147 In study (i):

a) only 12 female animals (i.e., less than 20 female animals) with implementation sites are included in each group, and therefore the statistical power is not equivalent to OECD TG 414;
b) the foetuses are not examined for sex and body weight; the foetuses are not examined for external, skeletal and soft tissue alterations (variations and malformations); number of resorptions and/or live foetuses are not investigated;

anogenital distance is not measured in live rodent foetuses.

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

149 On this basis, the study is not adequate for the information requirement.

*8.2.2. Read-across adaptation rejected*

150 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.

151 Therefore, studies (ii) and (iii) cannot be used to adapt this information requirement.

*8.2.3. No legal basis for the adaptation*

152 A registrant may only adapt this information requirement based on the specific rules for adaptation set out in Column 2 of Annex X, section 8.7., or the general rules for adaptation set out in Annex XI.

153 The argumentation provided in your comments to the draft decision does not refer to any legal ground for adaptation under Annex XI to REACH nor to any specific rules set out in Column 2 for this standard information requirement. In addition, even if, with your comments, you agree with study requests 2 and 3 of the present decision and propose to use these studies in support of your adaptation, these studies are yet to be conducted.

154 You also intend to use the requested 90-day repeated dose toxicity study to identify the tolerated dose levels and set the testing doses for the pre-natal developmental study in rats. However, ECHA notes that there is a significant difference in the exposure period between the two studies (20 days for the pre-natal development study). Furthermore, toxicity, toxicokinetics and sensitivity in pregnant animals, as those to be used in a pre-natal developmental study, may differ from those in non-pregnant animals, as those normally tested in a repeated dose toxicity study. Therefore, selection of the highest dose level for the pre-natal developmental study based solely on the 90-day repeated dose toxicity study may not be fit for purpose.

155 Moreover, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under Column 2 nor under the general rules of Annex XI.

156 Overall, ECHA cannot currently assess or conclude on the validity of your intended adaptation. ECHA has also doubts about the usefulness of the requested 90-day repeated dose toxicity study in rats for the dose-level setting for the pre-natal developmental study in rats.

157 Therefore, you remain responsible for complying with this decision by the set deadline.

158 Please note, however, that the deadline given in this decision allows for sequential testing for the two pre-natal developmental toxicity studies requested under sections 3 and 8, including the possibility to perform preliminary dose-range finding studies.

159 Based on the above, the information requirement is not fulfilled.

*8.3. Specification of the study design*

160 A PNDT study according to the test method OECD TG 414 should be performed in rabbit or rat as preferred second species. The study in the first species is to be carried out by using a non-rodent species (rabbit) (request 3 in this decision).

161 Therefore, a PNDT study in a second species must be performed in the rat as preferred rodent species.

162 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex X, Section 8.7.2., Column 1).

163 Based on the above, the study must be conducted in rats with oral administration of the Substance.

**References**

The following documents may have been cited in the decision.

***Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)***

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

***Guidance on data-sharing***; ECHA (2017).
**Guidance for monomers and polymers**; ECHA (2012).
**Guidance on intermediates;** ECHA (2010).
All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

***Top-dose selection; ECHA (2022)***

The advice document is available online:
https://echa.europa.eu/documents/10162/17220/211221_echa_advice_dose_repro_en.pdf

***Read-across assessment framework (RAAF)***

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017).
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs; ECHA (2017).
The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

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

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

**Appendix 2: Procedure**

The information requirement for an Extended One-Generation Reproductive Toxicity Study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. The EOGRTS may be addressed in a separate decision once the information from the sub-chronic toxicity study (90 days) requested in this decision is provided; because the results from the 90-day study are needed for the design of the EOGRTS.

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 04 August 2022.

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

ECHA took into account your comments and did not amend the request(s) or the deadline.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.
In your comments to the draft decision you considered "*Due to the high demand, we see that the testing laboratories are facing severe delays in the performance and reporting of the studies. We would like to request a six months extension of the deadline which we believe will allow us to perform the studies and submit the updated dossier in a timely manner.*" You did not provide any justification from a test laboratory to support your request for an additional 6-months extension of the deadline. As explained above, ECHA has already extended the deadline by 12 months.

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.

Following the Board of Appeal's decision in case A-001-2022 ECHA revised the study design specifications for meeting the information requirement for simulation testing on ultimate degradation in surface water (Annex VIII, column 2, section 9.2 and/or Annex IX, first column, section 9.2.1.2).

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

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

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

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

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

(5) 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.

(6) 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.

(7) 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[2].

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

### 1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values.

[2] https://echa.europa.eu/practical-guides

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

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