~~Confidential~~

Helsinki, 06 September 2022

Addressees
Registrant(s) of JS_25134-21-8 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
01/05/2018

Registered substance subject to this decision ("the Substance")
Substance name: 1,2,3,6-tetrahydromethyl-3,6-methanophthalic anhydride
EC number: 246-644-8

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***15 September 2025***.

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

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

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

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

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

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

5. 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.

6. Identification of degradation products (Annex IX, 9.2.3.; test method: using an appropriate test method)

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.

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

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0. Reasons common to several requests

0.1. Assessment of the read-across approach provided in the comments to the draft decision

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

- 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.)

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 ecotoxicological properties

5 You provide a read-across justification document in the comments to the draft decision.

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

MTHPA methyltetrahydrophthalic anhdride, EC No 234-290-7.

7 You provide the following reasoning for the prediction of ecotoxicological properties: "*the target and source substances have qualitatively similar properties in toxicological and (eco)toxicological studies based on their similar structure and identical functional groups resulting in common metabolites.*" You further indicate that "*The read-across hypothesis is that different substances give rise to qualitatively similar properties to which the organism is exposed (Scenario 2, RAAF).* [..] *Moreover, that the properties of the target substance can be predicted to be quantitatively equal to those of the source substance.*"

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.

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

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

10 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide

supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

11 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 source substance(s) is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from supporting information/bridging studies of comparable design and duration for the Substance and for the source substance(s). In order to support your hypothesis, in the comments to the draft decision you refer to the following:

a. For the source substance MTHPA, you refer to the OECD TG 211 study used in the prediction for long-term toxicity to aquatic invertebrates in the registration dossier. Furthermore, for MTHPA you report descriptions on study design and results of the the prolonged toxicity to fish (OECD TG 204) study used in the prediction for long-term toxicity to fish in the comments to the draft decision. You consider that the results of the OECD TG 211 and OECD TG 204 studies on the source substance MTHPA indicate "*lack of long-term toxicity*" for MTHPA.

b. You refer to the OECD TGs 203, 202 and 201 studies on the Substance in the registration dossier and provide descriptions on study design and results of OECD TGs 203, 202 and 201 studies on the source substance MTHPA in the comments to the draft decision. You consider that the results of the short-term toxicity to fish and to aquatic invertebrates studies (OECD TG 203 and 202, respectively) on the Substance are consistent with those on the source substance MTHPA, indicating no hazards (e.g. L(E)C50s > 100 mg/L). In addition, you consider that the results of the algae growth inhibition studies (OECD TG 201) on the Substance (72h-ErC50 > 100 mg/L, NOErC 66.7 mg/L) and on the source substance MTHPA (72h-ErC50 = 68 mg/L; NOErC 27.5 mg/L) indicate that "*the source substance has been found to be slightly more toxic than the target substance with immediate relevance to algae.*"

c. You provide QSAR predictions (US EPA ECOSAR v.2.0, Chemical Class: Neutral Organics) for short-term and long-term aquatic toxicity endpoints "*for METH* [the Substance] *corresponding isomers and dicarboxylic acids*" (Table 12 of the justification document) and "*for MTHPA corresponding isomers and dicarboxylic acids*" (Table 13 of the justification document). You consider that "*ECOSAR predicts similar values for MTHPA and METH as well as similar values for the MTHPA and METH hydrolysis products* [i.e. the corresponding dicarboxylic acids]".

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

a. You refer to the results of the long-term toxicity to aquatic invertebrates (OECD TG 211) study and of the prolonged toxicity to fish study (OECD TG 204) on the source substance MTHPA. The latter cannot be regarded as a long-term fish test as explained further below under the relevant information requirement section 4.3.1.1, thus this study cannot be use to conclude on the long-term toxicity to fish properties of the source substance MTHPA. Furthermore, while you provide these studies on the source substance MTHPA, your registration dossier and the read-across justification provided in the comments do not include any robust study summaries or descriptions of data for the Substance that would confirm that both substances cause the same type of effects for the properties under consideration, as also explained in points b-c) below.

b. You refer to the results of OECD TGs 203, 202 and 201 studies on the Substance and on the source substance MTHPA, which inform on fish mortality, immobilisation of daphnids and algae growth inihibition, respectively. However, you have provided no justification nor evidence on how this information is relevant for the prediction of long-term effects to fish (on growth and development) and of long-term effects to aquatic invertebrates (on development and reproduction) for the Substance, as investigated in the requested studies according to the OECD TGs 210 and 211 respectively. In the absence of adequate information allowing to compare the properties of the Substance and of the source substance, it cannot be confirmed that both substances cause the same type of effects.

c. You refer to the results of QSAR predictions for short-term and long-term aquatic toxicity endpoints, which you have provided for the isomers of the Substance and of the source substance MTHPA, as well as for the isomers of their hydrolysis products (corresponding dicarboxylic acids). While not explicitly specified by you, ECHA understands that the models you used for the prediction are for the Chemical Class: Neutral Organics (US EPA ECOSAR v.2.0). Due to the rapid hydrolysis of the Substance and of the source substance MTHPA (i.e. half-lives < 7 min and 3.5 min, respectively, as reported in the justification document), it is relevant to provide data on aquatic toxicity of their hydrolysis products. However, the provided QSAR predictions for the hydrolysis products are not reliable for the same reasons as explained further below under sections 4.3.2.1 and 4.3.2.2. Specifically, you have provided no information on the closest analogues and the hydrolysis products (i.e. dicarboxylic acids) are ionisable and thus are not in the applicability domain of the model (i.e. US EPA ECOSAR v.2.0, Chemical Class: Neutral Organics).

13 Thus the data set reported in the dossier and in the comments to the draft decision does not include relevant, reliable and adequate information for the Substance and the source substance(s) to support your read-across hypothesis.

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

0.1.2. Conclusion on the read-across approach

15 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 IX of REACH

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

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

1.1. Information provided

17 You have provided:

(i) Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test with the Substance (2012)
(ii) A waiving statement based on skin and respiratory sensitizing properties regarded to be the most sensitive endpoints of the Substance

1.2. Assessment of the information provided

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

1.2.1. Study not adequate for the information requirement

19 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. dosing of the Substance daily for a minimum of 90 days;
b. haematological and clinical biochemistry tests as specified in paragraphs 30-38 of the test guideline;
c. the oestrus cycle in females at necropsy;
d. terminal organ and body weights;
e. gross pathology as specified in paragraphs 43-46 of the test guideline;
f. full histopathology as specified in paragraphs 47-49 of the test guideline.

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

a. the exposure duration is only 41 - 47 days;
b. data on haematology and clinical biochemistry findings are missing: T4, T3 and TSH measurements were not performed;
c. data on oestrus cycle are missing;
d. data on terminal organ weights are available for 5 males/5 females instead of 10 males/10 females;
e. data on gross pathology findings are missing: incidence and severity; in particular, the following investigations are missing: examinations were performed on 5 males/5 females instead of 10 males/10 females;
f. data on histopathology findings are missing: incidence and severity. In particular,

the following investigations are missing: examinations were performed on 5 males/5 females instead of 10 males/10 females.

21 The information provided does not cover the key parameters required by the OECD TG 408. Therefore, the study is rejected.

1.2.2. Your justification to omit the study does not refer to any adaptation possibilty

22 Standard information requirements may be adapted according to the specific rules of adaptation in Column 2, Annex IX, section 8.6.2. or the general rules of Annex XI.

23 You have not provided any specific legal reference for your adaptation of this information requirement.

24 You informed in your waiving statement (ii) that "*Data are available from a study of shorter duration (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted according to OECD 422) in which the substance was administered by gavage at doses of 0, 7, 20 and 50 mg/kg/day for 42 days. Post mortem macroscopic observations, absolute and relative organ weights and microscopic examination did not show any changes indicative of systemic toxicity of the substance other than effects in the kidneys. These findings were possibly due to a pH effect of the substance which hydrolyses to the corresponding acid*."

25 As stated above, the study is rejected.

26 In waiving statement (ii) you also stated, that "*The substance is classified as both a skin and respiratory sensitiser in accordance with the requirements of Directive 67/548/EEC (DSD) and Regulation 1272/2008 (CLP). As such, sensitisation is to be regarded as the most sensitive end-point for which no DNEL can be derived due to the lack of dose-response data. Instead, a qualitative approach must be applied to assess and control risks (in accordance with "Guidance on information requirements and chemical safety assessment, Chapter R8: Characterisation of dose(concentration)-response for human health")".*

27 ECHA understands that your justification to omit this information refers to the argument that a qualitative approach must be applied to assess and control risks based on the most sensitive end-point which is sensitisation, for which no DNEL can be derived.

28 However, this justification does not relate to the specific rules for adaptation under Column 2, Annex IX, Section 8.6.2. In addition, your justification does not refer to any legal ground for adaptation under Annex XI to REACH.

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

1.2.3. Animal welfare

30 You concluded "*With consideration of these aspects, together with the available information of the OECD 422 sub-acute study, further testing would not be in line with current concerns regarding animal welfare and the use of animals in scientific experiments*."

31 However, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

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

1.3. Information provided in the comments to the draft decision

33 In the comments to the draft decision you refer to the respiratory sensitisation properties of the Substance requiring stringent risk management measures (RMMs) to ensure workers protection. You specify that "*the substance is exclusively handled at industrial settings with the required engineering and use of personal protection equipment*" and you consider that "*exposure of professionals and consumers of the substance does not occur*". On that basis you conclude that "*further studies using mammalians to evaluate human health endpoints would not result in any change of the existing RMMs*".

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

35 In its decision on the case A-015-2019, the Board of Appeal considered that the fact that stringent risk management measures are in place to protect users from the sensitisation hazard do not affect the registrant's obligation to provide information on other endpoints, assess all the risks related to the substance, and develop appropriate risk management measures with regard to all those risks, and not only to respiratory sensitisation (Paragraph 45 of the ECHA Board of Appeal decision, case A-015-2019[2]). Therefore, your considerations that "*further studies using mammalians to evaluate human health endpoints would not result in any change of the existing RMMs*" do not constitute acceptable adaptation for the information requirement of Annex IX, 8.6.2.

1.4. Test selection

36 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.

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

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

2. Pre-natal developmental toxicity study in one species

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

2.1. Information provided

40 You have provided:

(i) Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test with the Substance (2012)
(ii) A waiving statement based on skin and respiratory sensitizing properties regarded to be the most sensitive endpoint of the Substance

2.2. Assessment of the information provided

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

2.2.1. Study not adequate for the information requirement

42 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:

[2] Decision of the Board of Appeal, case No. A-015-2019

a) at least 20 female animals with implantation sites are included for each test and control group;
b) the dams are examined for any structural abnormalities, including gravid uterus weight;
c) the foetuses are examined for skeletal and soft tissue alterations (variations and malformations).

43 The study (i) is described as a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. This study has been conducted using the OECD TG 422 which is a screening test rather than a conclusive developmental toxicity study.

44 That study does not cover the key parameters of the OECD TG 414, because:

a) only 12 females were included in each test and control group;
d) data on the examination of the dams, in particular gravid uterus weight is missing;
b) skeletal and soft tissue alterations (variations and malformations) were not investigated.

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

2.2.2. Your justification to omit the study does not refer to any adaptation possibilty

46 Standard information requirements may be adapted according to the specific rules of adaptation in Column 2 , Annex IX, section 8.7.2. or the general rules of Annex XI.

47 You have not provided any specific legal reference for your adaptation of this information requirement.

48 You informed in your waiving statement (ii) that "*Data are available regarding effects on the potential developmental toxicity of 1,2,3,6-tetrahydromethyl-3,6-methanophthalic anhydride, these from a screening study (OECD 422) in which the substance was administered to rats daily at dose levels of 0, 7, 20 and 50 mg/kg/day. No adverse effects regarding developmental toxicity were apparent in this study*."

49 As stated above, the study is rejected.

50 In your waiving statement (ii) you also stated, that "*The substance is classified as both a skin and respiratory sensitiser in accordance with the requirements of Directive 67/548/EEC (DSD) and Regulation 1272/2008 (CLP). As such, sensitisation is to be regarded as the most sensitive end-point for which no DNEL can be derived due to the lack of dose-response data. Instead a qualitative approach must be applied to assess and control risks (in accordance with "Guidance on information requirements and chemical safety assessment, Chapter R8: Characterisation of dose(concentration)-response for human health").*"

51 ECHA understands that your justification to omit this information refers to the argument that a qualitative approach must be applied to assess and control risks based on the most sensitive end-point which is sensitisation, for which no DNEL can be derived.

52 However, this justification does not relate to the specific rules for adaptation under Column 2, Annex IX, Section 8.7.2. In addition, your justification does not refer to any legal ground for adaptation under Annex XI to REACH.

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

2.2.3. Animal welfare

53 You concluded "*with consideration of these aspects, together with the available information from the OECD 422 study not suggesting a concern, further testing would not be in line with current concerns regarding animal welfare and the use of animals in scientific experiments.*"

54 However, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

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

2.3. Information provided in the comments to the draft decision

56 In the comments to the draft decision you refer to the respiratory sensitisation properties of the Substance requiring stringent risk management measures (RMMs) to ensure workers protection. You specify that "*the substance is exclusively handled at industrial settings with the required engineering and use of personal protection equipment*" and you consider that "*exposure of professionals and consumers of the substance does not occur*". On that basis you conclude that "*further studies using mammalians to evaluate human health endpoints would not result in any change of the existing RMMs*". ECHA understands that you refer to existing RMMs to omit the following information requirements: Sub-chronic toxicity study (90-day), Pre-natal developmental toxicity study in one species.

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

58 In its decision on the case A-015-2019, the Board of Appeal considered that the fact that stringent risk management measures are in place to protect users from the sensitisation hazard do not affect the registrant's obligation to provide information on other endpoints, assess all the risks related to the substance, and develop appropriate risk management measures with regard to all those risks, and not only to respiratory sensitisation (Paragraph 45 of the ECHA Board of Appeal decision, case A-015-2019[3]). Therefore, your considerations that "*further studies using mammalians to evaluate human health endpoints would not result in any change of the existing RMMs*" do not constitute acceptable adaptation for the information requirement of Annex IX, 8.7.2.

2.4. Test selection

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

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

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

3. Long-term toxicity testing on aquatic invertebrates

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

3.1. Information provided

[3] Decision of the Board of Appeal, case No. A-015-2019

63 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided the following justification: "*In accordance with REACH Regulation 1907/2006, Annex IX, Column 2, section 9.1 long-term tests on aquatic invertebrates do not need to be conducted as the Chemical Safety Assessment does not indicate the need to further investigate the effects of the substance and/or relevant degradation products. Upon contact with water hydrolysis to the corresponding dicarboxylic acid appears very rapidly and therefore, not long-term but acute toxicity effects are relevant. Moreover, the available information about production and processing of the substance, and the uses identified, indicates that direct releases to the aquatic compartment can be excluded*."

64 Furthermore, you have adapted this information requirement by using a Grouping of substances and read-across approach and provided the following information:

i. a study on long-term toxicity to aquatic invertebrates with the source substance MTHPA.

3.2. Assessment of the information provided

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

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

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

67 In the comments to the draft decision, you request ECHA to postpone the final decision on this standard information requirement in order to wait the decision of the General Court on a pending court case challenging the BoA decisions A-010-2018 and A-011-2018. Note that acts and decisions of EU Institutions and agencies are presumed lawful until they are declared void by the EU Courts. Therefore, while the court proceedings you are referring to in your comments are pending, the relevant findings of the Board of Appeal in case A-011-2018 remain fully applicable.

68 Your adaptation is therefore rejected.

3.2.1. Read-across adaptation rejected

69 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).

70 You have provided a robust study summary for a study conducted with another substance than the Substance in order to comply with this information requirement. In your dossier, 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).

71 You have provided such documentation in the comments to the draft decision, which is addressed in Section 0.1.

72 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.

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

3.3. Study design and test specifications

74 The Substance is difficult to test since it is hydrolytically unstable (hydrolysis half-lives in purified water range from 0.32 to 18 minutes at 20°C within a pH range of 9 to 4). The OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in the OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Considering that the Substance is rapidly hydrolysable, it is important to take into account the relative toxicities of the parent test chemical and hydrolysis products to determine the appropriate test design and test media preparation methods for the Substance. Taking the rapid hydrolysis of the parent substance into account, it may be difficult to achieve and maintain the desired exposure concentrations of the Substance or its hydrolysis products. Therefore, you must monitor the test concentration(s) of the Substance, or its hydrolysis products, throughout the exposure duration and report the results.

4. Long-term toxicity testing on fish

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

4.1. Information provided

76 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided the following justification: "*In accordance with REACH Regulation 1907/2006, Annex IX, Column 2, section 9.1 long-term tests on aquatic invertebrates do not need to be conducted as the Chemical Safety Assessment does not indicate the need to further investigate the effects of the substance and/or relevant degradation products. Upon contact with water hydrolysis to the corresponding dicarboxylic acid appears very rapidly and therefore, not long-term but acute toxicity effects are relevant. Moreover, the available information about production and processing of the substance, and the uses identified, indicates that direct releases to the aquatic compartment can be excluded.*"

4.2. Assessment of the information provided

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

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

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

79 In the comments to the draft decision, you request ECHA to postpone the final decision on this standard information requirement in order to wait the decision of the General Court on a pending court case challenging the BoA decisions A-010-2018 and A-011-2018. Note that acts and decisions of EU Institutions and agencies are presumed lawful until they are declared void by the EU Courts. Therefore, while the court proceedings you are referring to in your comments are pending, the relevant findings of the Board of Appeal in case A-011-2018 remain fully applicable.

80 Your adaptation is therefore rejected.

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

4.3. Information provided in the comments to the draft decision

82 In the comments to the draft decision, you do not agree to perform the long-term toxicity to fish study as requested in the draft decision. You have provided the following reasons to omit the study:

83 (i) First, you propose to adapt this information requirement by using Annex XI, Section 1.5. (Grouping of substances and read-across approach) based on experimental data from the following substance:

i. an OECD TG 204 study with the source substance MTHPA.

84 (ii) Second, you propose to adapt this information requirement by using Annex XI, Section 1.3. (Qualitative or Quantitative Structure-Activity Relationships, (Q)SARs). To support the adaptation, you have provided the following information:

ii. predictions from US EPA ECOSAR v2.0 (Chemical Class: Neutral Organics) for the "*corresponding isomers and dicarboxylic acids*" of the Substance (i.e. 5- METHAc and 4- METHAc).

85 (iii) Third, ECHA understands that you also propose to waive this information requirement since the Substance is "*not expected to be harmful to fish from a chronic or long-term exposure perspective*" based on the following arguments:

- Short-term tests with the Substance and long-term tests with the source substance MTHPA indicate lack of hazards to aquatic organisms.
- The updated Chemical Safety Assessment (CSA) (document attached to the draft decision) "*shows results for environmental toxicity based on data from a Daphnia magna study, and thus, fish study is considered to be not needed*".
- The UK Health and Safety Executive (HSE) "*evaluated this in different cases and found that the Daphnia magna has already covered this, and therefore, the fish should only be performed if the RA* [Risk Assessment] *based on the Daphnia magna asserts that it is not safe.*"

86 (iv) Finally, you consider that "*long-term toxicity testing on fish should therefore not be carried out to avoid unnecessary testing on vertebrate animals*".

87 ECHA has assessed the information provided in the comments and identified the following issue(s):

4.3.1. Read-across adaptation (i) rejected

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

4.3.1.1. Missing robust study summary

89 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.

90 In your justification document you have identified the source study (study i. above) but provided only the effect values and information on the study method (i.e. OECD TG 204).

91 You have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the study. 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.

4.3.1.2. Source study not adequate for the information requirement

92 Under Annex XI, Section 1.5., the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

93 To be adequate for the purpose of classification and labelling and/or risk assessment in relation to the current information requirement, a study must be a long-term fish test. Guidance on IRs and CSA, Section R.7.8.4.1. specifies that only studies in which sensitive life-stages (juveniles, eggs and larvae) are exposed can be regarded as long-term fish tests.

94 In your justification document you have identified the source study (study i. above) according to OECD TG 204 in which fish were exposed to the test material.

95 The study i. does not provide information on the toxicity of the test material to all relevant sensitive life-stages (i.e. including eggs and larvae). OECD TG 204 only provides information on prolonged acute toxicity and, based on the above, it does not qualify as a long-term fish test.

96 Therefore, the provided study is not adequate for classification and labelling and/or risk assessment purposes.

4.3.2. (Q)SAR adaptation (ii) rejected

97 Under Annex XI, Section 1.3., the following condition (among others) must be fulfilled whenever a (Q)SAR approach is used:

(1) the substance must fall within the applicability domain of the model.

98 With regard to this condition, we have identified the following issue(s):

4.3.2.1. Inadequate documentation of the prediction (QPRF)

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

100 You provided QPRFs for the predictions. The information you provided about the prediction lacks information on the close analogues.

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

4.3.2.2. The substance is outside the applicability domain of the model

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

103 In the provided (Q)SAR Model Reporting Format document (QMRF), you report that the applicability domain of the model you used is defined as *"non-reactive, non-ionizable neutral organic compounds and solvents"* (ECOSAR v2.0, Chemical Class: Neutral Organics).

104 The structures used as input for the predictions (study ii. above) have the following properties related to the estimation of applicability domain: 5- METHAc and 4- METHAc (i.e. the *"corresponding isomers and dicarboxylic acids"* of the Substance) ionise at environmentally relevant pHs, since in the dossier you report pKa1 = 4.42 and pKa2 = 6.93 for each acid.

105 Due to the rapid hydrolysis of the Substance (i.e. half-life 0.32 to 18 minutes at 20°C within a pH range of 9 to 4), it is relevant to provide data for the hydrolysis products. However, the structures used as input for the predictions are ionisable and therefore are not neutral organic compounds.

106 Therefore, you have not demonstrated that the Substance (its hydrolysis products) falls within the applicability domain of the model.

107 Based on the above, your adaptation is rejected.

4.3.3. Your arguments (iii) and (iv) to omit the study do not refer to any adaptation possibility

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

109 Your justification (iii) to omit this information refers to expected lack of chronic hazards to fish and to the risk assessment (in the updated CSA and in UK ESA) not showing the need for further long-term fish testing based on data on aquatic invertebrates. Your justification (iv) refers to minimisation of vertebrate testing.

110 The arguments do not refer to any of the adaptation possibilities in Annex XI.

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

4.4. Study design and test specifications

112 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.).

113 The OECD TG 210 specifies that, for difficult to test substances, the 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 3.

5. Simulation testing on ultimate degradation in surface water

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

5.1. Information provided

115 You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.2.1.2., Column 2. In support of your adaptation, you provided the following justification: *"In accordance with REACH Regulation 1907/2006/EC (Annex IX - 9.2.1.2 & 9.2.1.4 - column 2) simulation testing on biodegradation in surface waters and sediment does not need to be conducted as direct or indirect exposure of the aquatic and terrestrial compartments for this substance are unlikely. The substance is hydrolysed rapidly in a few*

minutes to the corresponding dicarboxylic acid. In addition, based on the intended uses, exposure of sediments is not likely."

5.2. Assessment of information provided

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

5.2.1. Your justification to omit the study does not refer to any adaptation possibility

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

117 Your justification to omit this information refers to unlikely exposure of the aquatic and sediment compartment and to rapid hydrolysis, which are not specific rules for adaptation under Column 2, Annex IX, Section 9.2.1.2.. In addition, your justification does not refer to any legal ground for adaptation under Annex XI to REACH.

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

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

5.3. Study design and test specifications

120 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.

121 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.).

122 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.

123 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.

124 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.).

6. Identification of degradation products

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

6.1.1. You have provided no information

126 You have provided information on the identity of the hydrolysis products, but no information on the identity of further transformation/biodegradation products for the Substance.

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

6.2. Study design and test specifications

128 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 Request 5 or by some other measure. If any other method is used for the identification of the transformation/degradation products, you must provide a scientifically valid justification for the chosen method.

129 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Request 5) 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).

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 16 June 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).

Request for deadline extension

In the comments to the draft decision, you requested an extension of the deadline from 18 to 36 months from the date of adoption of the decision. You justified the request by the complexity and duration of the studies and by additional time needed to commence the studies due to laboratory capacity. Based on the documentary evidence provided, ECHA has agreed with your request for a deadline extension and has extended the deadline to 36 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.

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

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

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[4].

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

1.2. Test material

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

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values 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 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[5].

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