~~Confidential~~

Helsinki,01 December 2022

Addressees
Registrant(s) of MTHPA_234-290-7 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
14/06/2016

Registered substance subject to this decision ("the Substance")
Substance name: Tetrahydromethylphthalic anhydride
EC number: 234-290-7

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 information listed below by ***9 March 2026***.

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

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

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

2. 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.

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

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

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

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

Contents

Reasons related to the information under Annex IX of REACH

1. Long-term toxicity testing on fish

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

1.1. Information provided

2 You have provided

(i) an OECD TG 204 study (1997) with the Substance in your registration dossier.

3 In your comments on the draft decision, you propose to adapt this standard information requirement by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2, using the existing toxicity data and:

(ii) (Q)SAR (ECOSAR v.2.0) to predict chronic fish and daphnia toxicity.

4 You have also provided statements claiming that *Daphnia* is more sensitive than fish using QSAR predictions and experimental information on *Daphnia* (OECD TG 202 and 211) and fish (OECD TG 203 and 204).

1.2. Assessment of the information provided

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

1.2.1. The OECD TG 204 is not a valid test guideline to meet this information requirement

6 To fulfil the 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.

7 Your registration dossier provides an OECD TG 204 study in which only juveniles were exposed to the test material.

8 This study does not provide information on the toxicity of the test material to all relevant sensitive life-stages (i.e. juveniles, 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. Therefore, this information is rejected.

9 In the comments to the draft decision, you agree that provided prolonged toxicity test in fish according to OECD TG 204 (performed on the source substance MTHPA generic) does not sufficiently meet the information requirement of Annex IX, Section 9.1.6. However, you do not agree that a new study needs to be performed and propose a weight-of-evidence adaptation ((Annex XI, Section 1.2.)) using the existing toxicity data and QSAR. Weight-of-evidence adaptation

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

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

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

13 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 9.1.6. includes similar information that is produced by the OECD TG 210. This includes parameters related to the survival and development of fish in early life stages from the stage of fertilized egg until the juvenile life-stage following exposure to the test substance are measured, including:

1. the stage of embryonic development at the start of the test, and
2. hatching of fertilized eggs and survival of embryos, larvae and juvenile fish, and
3. the appearance and behaviour of larvae and juvenile fish, and
4. the weight and length of fish at the end of the test.

14 First, your statements regarding sensitivity of *Daphnia* and fish cannot be taken into account in the assessment of your weight of evidence adaptation because they do not provide any relevant information for this information requirement, i.e., relating to survival and development of fish in early life stages in long-term exposure.

Key parameters 1, 3-4

15 The source of information (i) does not provide relevant information on the stage of embryonic development at the start of the test, the appearance and behaviour of larvae and juvenile fish, and the weight and length of fish at the end of the test.

16 The source of information (ii) may provide relevant information on these parameters.

17 However, the reliability of this source of information is significantly affected by the following deficiency:

18 Under Annex XI, Section 1.3., the substance must fall within the applicability domain of the model whenever a (Q)SAR approach is used.

19 Under Guidance on IRs and CSA R.6.1.5.3., a prediction is within the applicability domain of the model, when, among others, the substance and the structures selected for the prediction fall within descriptor, structural, mechanistic and metabolic domain.

20 In the (Q)SAR Model Reporting Format document (QMRF) which you submitted in the comments on the draft decision, you report the following applicability domain for the model you used: "ECOSAR's chemical class of Neutral Organics, which are defined as non-reactive, non-ionizable neutral organic compounds and solvents".

21 The Substance have the following properties related to the estimation of applicability domain:

- hydrolysed diacid form of the constituents of the Substance ([redacted]) ionise at environmentally relevant pHs, since in the dossier you report pKa #1=3.86-3.94 and pKa#2=5.63-5.70 at 25 degree C (range given for different isomeric forms of MTHP);
- Hydrolysed diacid forms of the constituents of the Substance ([redacted]) are reactive since in the "Read-across justification report for MTHPA generic (CAS 11070-44-3; EC 234-290-7)" submitted in the comments on the draft decision you report "Reactive unspecified" and "Class 3

(unspecific reactivity)" structural alerts (MOA by OASIS and Acute aquatic toxicity classification by Verhaar).

22 Due to the rapid hydrolysis of the Substance (i.e. hydrolysis half-life at 25°C within a pH range of 5-9 is < 24 hours), it is relevant to provide data for the hydrolysis products. However, the structures used as input for the predictions are ionisable and reactive, therefore are not neutral organic compounds.

23 Therefore, you have not demonstrated that the Substance (its hydrolysis products) falls within the applicability domain of the model, and the condition of Annex XI, Section 3 is not met.

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

Key parameter 2

25 The source of information (i) may provide relevant information on mortality of juvenile fish. However, this source of information does not provide relevant information on hatching of fertilized eggs and survival of embryos and larvae. Furthermore, even the information on the mortality of juvenile fish contains uncertainty because mortality is observed over a considerably shorter exposure duration (14 days) than in a long-term study (28-60 days post-hatch).

26 The source of information (ii) may provide relevant information on hatching of fertilized eggs and survival of embryos, larvae and juvenile fish. However, for the reasons specified under Key parameters 1, 3-4, the source of information (ii) is considered unreliable and cannot contribute to the conclusion on this key parameter investigated by the required study.

27 In summary, the sources of information (i) to (ii) provide relevant information on the survival and development of fish in early life stages from the stage of fertilized egg until the juvenile life-stage. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for long-term toxicity testing on fish.

28 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for long-term toxicity testing on fish. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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

1.3. Study design and test specifications

30 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.).

31 The Substance is difficult to test due to its hydrolysable properties (i.e. Hydrolysis half-life at 25°C within a pH range of 5-9 < 24 hours). OECD TG 210 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 210. 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.

2. Simulation testing on ultimate degradation in surface water

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

2.1. Information provided

33 You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.2.1.2. & 9.2.1.4, Column 2.: "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."

2.2. Assessment of information provided

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

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

35 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..

36 Your justification to omit this information refers to unlikely exposure of the aquatic and sediment compartment (Column 2, Annex IX, Section 9.2.1.4) and to rapid hydrolysis, which are not specific rules for adaptation for simulation testing on ultimate degradation on surface water 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.

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

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

2.3. Study design and test specifications

39 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.

40 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.).

41 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.

42 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.

43 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.).

3. Identification of degradation products

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

3.1.1. You have provided no information

45 You have provided no information on the identity of the degradation products for the Substance.

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

3.2. Study design and test specifications

47 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 Kow and potential toxicity of the transformation/degradation may need to be investigated. You must obtain this information from the degradation study requested in Request 2.

48 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

4. Pre-natal developmental toxicity study in a second species

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

4.1. Information provided

50 While you have not provided a specific legal reference for your adaptation of this information requirement, ECHA understands that you have adapted this information requirement by using weight of evidence based on the following experimental data:

i. A combined repeated dose and reproduction toxicity study with the Substance (1997);

51 In your justification of your adaptation you also refer to the following lines of information:

ii. a study in mice with oral administration of the analogue substance trimellitic anhydride (TMA) to mice during gestation days 7-14 (1983);

iii. a study in guinea pigs with inhalation exposure to the analogue substance trimellitic anhydride (TMA) during gestation days 6-15 (1988);

iv. A scientific publication on studies in mice with intra-peritoneal exposure to the analogue substances phthalic anhydride and succinic anhydride during gestation days 8-10 (Fabro S, 1982);

v. A scientific publication on a study in rats with the analogue substance maleic anhydride during gestation days 6-15 (Short RD, 1986);

vi. A scientific publication on a two-generation study in rats with the analogue substance maleic anhydride (Short RD, 1986).

52 You conclude from this information that "*The available data for structural homologues of tetrahydromethylphthalic anhydride (MTHPA) indicate neither potential for teratogenic effects nor for reproduction toxicity in different species. These data together with the available information of the OECD 422 study allow a scientific validated evaluation of the respective endpoints and further tests would not be in line with animal welfare ideas*".

53 In your comments on the draft decision, you have provided a new read-across justification and additional sources of information on the analogue substance 4-MHHPA (EC No. 243-072-0):

vii. a pre-natal developmental toxicity stuyy (OECD TG 414) conducted in rats with 4-MHHPA.

viii. a screening study for reproductive and developmental toxicity (OECD TG 421) conducted in rats with 4-MHHPA.

4.2. Assessment of the information provided

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

55 You have adapted this standard information requirement by applying weight of evidence (WoE) adaptation(s) under Annex XI, Section 1.2:

56 Your weight of evidence adaptations are based on information obtained from the Substance itself and from analogue substances structurally similar to the Substance.

4.2.1. Missing weighing of the sources of information

57 Annex XI, Section 1.2. requires a reasoned justification which explains why information from several independent sources together enable a conclusion on the information requirement. This justification must explain how the individual sources of information are weighted and how all the sources of information together enable a conclusion on each of the key parameters foreseen by the study normally required for the information requirement.

58 According to the Guidance on IRs and CSA, Section R.4, the weight given to the sources of information is influenced by the reliability of the data, consistency of results, nature and severity of effects, and relevance and coverage of the information for the given information requirement. The reliability of the data is strongly linked to the method used to generate the information. Therefore, aspects such as exposure duration, dose-levels used, and the statistical power of the study affect the weight of the individual sources of information.

59 Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be integrated in order to decide whether they together provide sufficient weight to conclude whether the Substance has or has not the (dangerous) property investigated by each of the key parameters foreseen by the study normally required for the information requirement. As part of the overall conclusion, an assessment of the residual uncertainty is also required.

60 You have provided the following justifications for the weight of evidence adaptation as follows:

- "*The available data for structural homologues of tetrahydromethylphthalic anhydride (MTHPA) indicate neither potential for teratogenic effects nor for reproduction toxicity in different species. These data together with the available information of the OECD 422 study allow a scientific validated evaluation of the respective endpoints and further tests would not be in line with animal welfare ideas*".

61 You have not weighted the individual sources of information nor provided a clear and transparent assessment of to which extent the sources of information cover each of the key parameters foreseen by the study normally required for the information requirement.

4.2.2. Missing robust study summaries

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

63 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)).

64 In your justifications of your adaptations you provide short descriptions of sources of information on analogue substances (listed above) that you include in your weight of evidence approaches. You also indicated that some of the studies were conducted by [redacted]

65 However, you have not provided individual endpoint study records in the form of robust study summaries (RSS) for any of these studies. You have not provided in your dossier detailed information on the methods, results and conclusions, allowing for an independent assessment of these studies.

66 In addition, studies conducted by [redacted] during the 1960's until 1978 have significant problems in their reliability. ECHA considers these studies as potentially invalid and the findings unreliable, unless formally audited by EPA / FDA post-hoc programme and the audit did not uncover any problems.

67 Therefore, the RSSs for [redacted] studies must include the conclusions of the audit report.

68 In the absence of RSS, and the above conclusion if relevant, the coverage of the key parameters by these sources and the reliability of their contribution on these parameters to your weight of evidence adaptations cannot be evaluated.

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

70 In your comments you have provided robust study summaries for the studies conducted with 4-MHHPA and the Substance, i.e. studies i., vii. and viii.

71 However, no Robust study summaries have been provided for the other sources of information relied on in the weight of evidence.

4.2.3. Reliability of the contribution of the information on analogue substances

72 ECHA understands that you use data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation. For this information to reliably contribute to the weight of evidence approaches, it would have to meet the requirements for Grouping of substances and read-across approaches.

73 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used.

74 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.

75 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).

76 Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

77 You provide a read-across justification in separate endpoint study records under sections 7.5.1 and 7.8.2 in IUCLID and in the respective sections of your Chemical Safety Report.

78 You provide the following reasoning for the predictions of toxicological properties in the endpoint study record provided for this adaptation: "*MTHPA is a cyclic anhydride and many cyclic anhydrides have a similar structure, containing a bicyclic ring structure with the carboxylic acid anhydride group being the reactive and toxicologically functional moiety. The bicyclic ring structure may be saturated or partially unsaturated and may contain*

[2] ECHA Guidance R.6
[3] Read-Across Assessment Framework (RAAF)
[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs

substituted methyl derivatives. Substances with substituted methyl groups may exist as several isomeric forms."

79 In your comments on the draft decision, you have provided a new read-across justification document "[redacted]" to justify the prediction of properties of the Substance.

80 You argue that 4-MHHPA and MTHPA are expected to have similar toxicological properties.

81 ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substances.

82 In addition to the critical shortcomings identified in section 4.2.2 above, ECHA notes the following additional shortcomings with regards to the reliability of the contribution of the information of the analogue substances to your weight of evidence adaptations.

4.2.3.1. Missing supporting information

83 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.).

84 Supporting information must include studies to compare properties of the Substance and of the analogue substances.

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

86 You have identified the presence of a carboxylic acid anhydride group in the structures of the Substance and of the source substances. You have also identified structural differences between the Substance and the source substances in that the biclyclic ring of the substances may be saturated or partially unsaturated and may contain substituted methyl derivatives.

87 Your read-across hypothesis assumes that the carboxylic acid anhydride group is the driver for the toxicological properties of these substances.

88 In your dossier, you report information from a combined repeated dose and reproduction toxicity study conducted with the Substance. In your justification of your adaptation, you also refer to existing information on analogue substances. However, as indicated in section 4.2.2. above, you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of these studies on analogue substances in your dossier.

89 As a consequence, these studies on analogue substances, as currently documented, do not constitute a basis for comparing the properties of the Substance and of the source substances. ECHA considers that you have not provided information establishing that the structural differences identified between the Substance and the source substances do not contribute to the toxicological properties of these substances.

90 As indicated above, you have in your comments provided a new read-across justification for read-across between 4-MHHPA and the Substance (MTHPA). To support your claim, you have provided robust study summaries of the available studies on Substance (OECD TG 422) and source substance 4-MHHPA (OECD TG 407, 408, 421 and 414) which support that MTHPA and 4-MHHPA have quantitatively and qualitatatively similar effects.

91 ECHA considers that the read-across justification together with the supporting robust study summaries on the Substance and the source substance 4-MHHPA constitute an adequate basis for predicting the properties of the Substance from 4-MHHPA.

92 However, the issues identified above remains for read-across to the other analogue substances.

93 In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties.

94 Therefore the information from the analogue substances other than 4-MHHPA cannot reliably contribute to your weight of evidence adaptations.

4.2.4. Relevance of the sources of information for the infromation requiremnt

95 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex X includes similar information that is produced by the OECD TG 414 on a second species (two species taking the first species into account to address the potential species differences). The following aspects are covered: 1) prenatal developmental toxicity in two species, 2) maternal toxicity in two species, and 3) maintenance of pregnancy in two species.

96 1) Prenatal developmental toxicity: Prenatal developmental toxicity includes information after prenatal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal) and other potential aspects of developmental toxicity due to in utero exposure. This information in two species should be covered to address the potential species differences.

97 2) Maternal toxicity: Maternal toxicity inlcudes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in the pregnant dam. This information in two species should be covered to address the potential species differences.

98 3) Maintenance of pregnancy: Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure.In your comments to the draft decision, you have provided new information in relation to the prenatal developmental toxicity and this information was found to address the relevant incompliance in the first species (Annex IX, 8.7.2.). In particular you have adapted this information in accordance with the grouping of substances and read-across approach (Annex XI, Section 1.5.), using the OECD TG 414 study conducted with 4-MHHPA, (accompanied by relevant read-across justification documents and necessary bridging information).

99 As the information requirement of a pre-natal developmental toxicity study in a first species is now fulfilled by data on the rat (i.e. the OECD TG 414 study conducted with 4-MHHPA), the second species must be a species other than rat.

100 Only three of the sources of information (studies ii. to iv.) bring information in other species than the rat.

101 For the reasons explained in the sections above, the sources of information (ii. to iv.) that are lacking robust study summaries cannot be considered as contributing for this aspect with any relevant and reliable information.

102 In addition, you have not established that these sources of information that are on analogue substances can predict the relevant property of the Substance.

103 ECHA concludes that there these sources cannot be considered as contributing for this aspect with any relevant and reliable information for pre-natal developmental toxicity in a second species.

104 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for pre-natal developmental toxicity srudi in a second species.

105 Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

4.3. Specification of the study design

106 A PNDT study according to the OECD TG 414 study should be performed in the rabbit.

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

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. This may be addressed in a separate decision.

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 amended the request(s).

You have provided comments during the decision-making phase which were found to address the incompliance identified in the draft decision. You included this information in an update of your registration dossier (submission number [redacted]). Therefore the original requests (In vitro cytogenicity study in mammalian cells or In vitro micronucleus study, Justification for an adaptation for Short-term repeated dose toxicity study (28d), Sub-chronic toxicity study (90-day), Pre-natal developmental toxicity study in one species) were removed.

In your comments to the draft decision, you requested additional time to conduct the environmental fate and hazard studies. You cite complexity of the testing and laboratory capacity as reasons for the extension.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. ECHA has considered your request and has extended the deadline by 12 months from the standard deadline to take into account currently longer lead times in contract research organisations.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: 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;
- 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[5].

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

1.2. Test material

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[6].

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