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Helsinki,01 December 2022

Addressees
Registrant(s) of JSub_5333-84-6 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
01 July 2020

Registered substance subject to this decision ("the Substance")
Substance name: 1,2,3,6-tetrahydro-3-methylphthalic anhydride
EC number: 226-247-6

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 ***9 March 2026***.

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

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020);

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202);

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201).

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

4. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487);

5. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490);

6. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats;

7. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203);

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

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

9. 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);

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

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

12. 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.

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.

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

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

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

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. Assessment of the read-across approach

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)
- 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 In your comments on the draft decision, you have proposed to adapt the additional information requirements by using grouping and read-across approach under Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

3 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.

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

5 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.

6 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.

7 In your comments on the draft decision, you raise a general read-across issue, noting that ECHA rejection of a read-across approach for information requirements appears inconsistent and contradictory as ECHA has accepted the read-across from the source substance MTHPA generic to the Substance for several information requirements related to environmental fate and toxicity.

8 Read-across justification must be endpoint specific. What constitutes appropriate supporting information and rationale for the approach depends on the endpoint being read-across (Guidance on IRs and CSA, Chapter R.6.2.2.1). Therefore, the read-across which is accepted for some information requirement does not automatically mean that it is accepted for other information requirements.

9 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 (eco)toxicological properties

10 You provide a read-across justification document in the IUCLID Sections of the relevant information requirements.

11 You predict the properties of the Substance from information obtained from the source substance tetrahydromethylphthalic anhydride (MTHPA), EC 234-290-7.

12 You provide the following reasoning for the prediction of (eco)toxicological properties. You describe the structural similarities of the Substance and the source substance MTHPA. You specify that the Substance "*is a specific isomer of the source substance, tetrahydromethylphthalic anhydride (MTHPA), in which neither the location of the double bond nor the methyl substitution are defined*" and highlight that the Substance is one of the constituents of the source substance MTHPA. You indicate that "*the physical and chemical properties do not show major differences*". You further refer to similarities in environmental fate and (eco)toxicological properties of cyclic anhydrides.

13 In your comments on the draft decision, you have provided read-across justification documents "[redacted]" and "[redacted]" to justify the prediction of properties of the Substance.

14 In your comments you provide the following reasoning for the prediction of (eco)toxicological properties from 4-MTHPA and MTHPA. You argue that read across from 4-MHHPA (EC No 243-072-0) to MTHPA generic is justified, and thus also to the Substance (3-MTHPA). 4-MHHPA, MTHPA and the Substance are expected to have similar (eco)toxicological properties."

15 You have provided a read-across justification for the read-across between MTHPA and 4-MTHPA supported with bridging information demonstrating that both substances have similar toxicity profiles.

16 You have also provided a separate read-across justification document for read-across between MTHPA and the Substance (3-MTHPA). You argue that the Substance accounts for around 50 % of the main isomers of the MTHPA and have provided QSAR predictions to support your claim that the remaining isomers in MTHPA are expected to have the same toxicity profile as the Substance.

17 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.to be quantitatively equal to those of the source substances.

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

0.1.1.1. Characterisation of the source substance

19 Annex XI, Section 1.5 of the REACH Regulation provides that "substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group."

20 Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substance(s) must be provided to allow assessing whether the attempted predictions are compromised by the composition and/or impurities.

21 In your dossier, you report that the Substance is a mono-constituent substance. In your read-across justification, you provide a qualitative description of the composition of the source substance, indicating that the Substance is a constituent of the source substance alongside other constituents. You do not provide quantitative information on the

concentration of the Substance and of the other constituents in the composition of the source substance.

22 Without quantitative information on the composition of the source substance, it is not possible to assess whether the attempted predictions are compromised by the composition of the source substance.

23 In the comments on the draft decision, you have provided further details to characterise the source substances. You claim that the *"target substance accounts for around 50 % of the main isomers of the source substance* [MTHPA, EC 234-290-7]*. In the other two main isomers of the source substance the methyl group is in the 4-position and the double bond in the 4- and 3- position, respectively*".

24 The read-across justification provided as part of your comments addresses the identified deficiency.

0.1.1.2. Test material representative for the source substance

25 Under Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

26 In order to predict the properties of the Substance, the test material used in the study on the source substance must be representative for the source substance (Article 10 and Recital 19 of REACH; Guidance on IRs and CSA, Section R.4.1.).

27 Therefore, the unambiguous characterisation of the composition of the test material used to generate the source data is required to assess whether the test material is representative for the source substance.

28 For the studies with the source substance provided for the ecotoxicological information requirements listed above, you have identified the test material as "[redacted]".

29 Furthermore, you indicate that the test material purity is 82.7g/eq (neutralization equivalent) and that free acid 0.5% is present as impurity. You do not provide information on the composition of the test material.

30 For the studies provided to fulfil the toxicological information requirements listed above, you have reported a test material purity of more that 99%. Such test material purity is not consistent with the description of the composition of the source substance provided in your read-across justification document whereby you indicate that it is composed of the Substance itself alongside other constituents.

31 In the absence of the information on the composition of the test material, you have not established that the test material used to generate the source data is representative for the source substance.

32 Therefore, the results from the source studies are considered not adequate for the purpose of classification and labelling and/or risk assessment.

33 In the comments on the draft decision, you have provided further information to justify the read-across to source substances. While you have not provided detailed description of the composition of the test material to address this deficiency, the additional information provided in the comments on the draft decision indicates that the issue is no longer relevant.

34 In particular, you argue that it is the carboxylic acid anhydride functionality common to the substances that drives the toxicity of the Substance (1,2,3,6-tetrahydro-3-methylphthalic anhydride, 3-MTHPA) and constituents of the source substances

tetrahydromethylphthalic anhydride (MTHPA generic; EC No. 234-290-7), as well as of the source substance hexahydro-4-methylphthalic anhydride (4-MHHPA; EC No. 243-072-0). You have provided robust study summaries of the available studies on the source substance MTHPA (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.

35 Based on the comparable studies with MTHPA generic and 4-MHHPA, ECHA considers it likely that these substances have similar properties.

36 For the Substance you have provided QSAR profiling of the isomers present both in the Substance (3-MTHPA) and MTHPA generic.

37 This information indicates that the other constituents (isomers) of the source substance MTHPA generic, are likely to have similar toxicity as the Substance and thus some (unknown) variation in the composition of the test material is unlikely to influence the toxicity observed in the source study.

38 Based on the above, the read-across justification and additional robust study summaries provided as part of your comments addresses the identified deficiency.

0.1.1.3. Adequacy and reliability of source studies

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

(1) be adequate for the purpose of classification and labelling and/or risk assessment;

(2) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;

(3) cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

40 Specific reasons why the studies on the source substance do not meet these criteria are explained further below under the applicable information requirement sections 4 and 11. Therefore, no reliable predictions can be made for these information requirements.

41 In your comments on the draft decision, you have provided Robust study summaries for in vitro cytogenicity studies (request 4) which addresses the issues regarding adequacy and reliability of the source study.

0.1.2. Conclusion on the read-across approach

42 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.

43 As described above, the read-across justification and additional robust study summaries provided as part of your comments addresses the deficiencies identified in your read-across approach (except the issue 0.1.1.3 for the request 11). However, as the information is currently not available in the registration dossier, all the identified deficiencies remain in the decision.

44 The registrants may therefore consider submitting this information in an updated registration dossier by the deadline set out in the decision.

0.2. Assessment of weight of evidence adaptations

45 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation(s) under Annex XI, Section 1.2:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.);
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.);

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

47 Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked.

48 Accordingly, ECHA addressed these deficiencies in the present Section, before assessing the specific standard information requirements in the following Sections.

0.2.1. Missing weighing of the sources of information for each information requirement

49 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.

50 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.

51 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.

52 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.

53 You have provided the following justifications for the weight of evidence adaptations as follows:

- For the information requirement for a sub-chronic (90-day) study: "*Taken all these data together, a 90 day toxicity study with MTHPA is not required and not in line with concerns regarding animal welfare and the use of animals for experimental purposes. The data available for similar substances in different species and for exposure periods of 90 days support the findings noted in OECD 422 study taking the time extrapolation factor into account. Therefore, the OECD 422 study is considered to represent a reliable basis for DNEL derivation for MTHPA isomers"*.
- For the information requirements for pre-natal developmental toxicity studies: "*The available data for structural homologues of MTHPA indicate neither potential for teratogenic effects nor for reproduction toxicity in different species. These data, together with the available information on MTHPA, allow a scientific validated evaluation of the respective endpoints and further tests would not be in line with concerns regarding animal welfare and the use of animals for experimental*

purposes".

54 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

0.2.2. Missing robust study summaries

55 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.

56 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)).

57 You have provided a robust study summary (RSS) only for a combined repeated dose and reproduction toxicity study (OECD TG 422) on the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC 234-290-7.

58 However, you have not provided individual endpoint study records in the form of robust study summaries for any of the studies conducted with other analogue substances.. In your justifications of your adaptations you provide only short descriptions of sources of information on analogue substances (listed under the specific information requirements below) that you include in your weight of evidence approaches. You also indicated that some of the studies were conducted by [redacted]

59 You have not provided in your dossier the detailed information on the methods, results and conclusions, allowing for an independent assessment of these studies. The assessment report from the WHO CICAD No 75 attached in your dossier does not provide any of these information on these studies either.

60 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.

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

62 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.

63 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.

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

64 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.

65 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).

66 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA and related documents.

67 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.

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

69 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.

70 In addition to the critical shortcomings identified in sections 0.2.1 and 0.2.2 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.

0.2.3.1. Missing supporting information

71 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.).

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

73 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).

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

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

76 In your dossier, you report information from a combined repeated dose and reproduction toxicity study conducted with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC 234-290-7. In your justification of your adaptations you also

refer to existing information on analogue substances, listed under the specific information requirements below. However, as indicated above in section 0.2.2, you have not provided in your dossier detailed information on the methods, results and conclusions, allowing for an independent assessment of the studies on the analogue substances other than for the study on MTHPA.

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

78 In the absence of such information, you have not established that the Substance and the analogue substance(s) are likely to have similar properties. Therefore the information from the analogue substances cannot reliably contribute to your weight of evidence adaptations.

79 Additional issues related to weight of evidence are addressed under the corresponding information requirements.

0.2.4. Information provided in your comments on the draft decision

80 In your comments to the draft decision, you have recognised the deficiencies noted for your weight of evidence adaptation (Annex XI, Section 1.2.) and you have proposed to adapt these information requirements in accordance with a grouping of substances and read-across approach (Annex XI, Section 1.5.). This adaptation has been analysed in section 0.1. above.

81 However, as the information is currently not available in the registration dossier, the deficiencies remain in the decision.

82 The registrants may therefore consider submitting this information in an updated registration dossier by the deadline set out in the decision.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

83 *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471 (2020).

1.1. Information provided

84 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided an OECD TG 471/472 study (1997) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7.

1.2. Assessment of the information provided

85 We have assessed this information and 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.

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

87 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1.

88 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

1.3. Specification of the study design

89 To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471, 2020) is considered suitable.

2. Short-term toxicity testing on aquatic invertebrates

90 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

2.1. Information provided

91 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided an OECD TG 202 study (1997) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7.

2.2. Assessment of the information provided

92 We have assessed this information and 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.

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

94 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1.

95 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

2.3. Study design and test specifications

96 The Substance is difficult to test since it is hydrolytically unstable. In your comments you have questioned the source of this statement. ECHA notes, that you state in your registration dossier that "*The cyclic anhydrides rapidly hydrolyse in contact with water*". To support your statement, you have provided a hydrolysis study on another cyclic anhydride (EC 234-290-7, hydrolysis half-lives in purified water range from 0.7 to 3.3 minutes at 20°C within a pH range of 9 to 4). Therefore it is likely that the Substance, which is also a cyclic anhydride, hydrolyses rapidly. OECD TG 202 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.

97 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.

98 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.

99 Therefore, you must monitor the test concentration(s) of the Substance, or its hydrolysis products, throughout the exposure duration and report the results.

3. Growth inhibition study aquatic plants

100 Growth inhibition study on aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

3.1. Information provided

101 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided an OECD TG 201 study (1997) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7.

3.2. Assessment of the information provided

102 We have assessed this information and 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.

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

104 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1.

105 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

3.3. Study design and test specifications

106 OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test.

107 Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 2.

Reasons related to the information under Annex VIII of REACH

4. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

108 An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII, Section 8.4.2..

4.1. Information provided

109 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided:

i. An *in vitro* mammalian chromosome aberration test according to the OECD TG 473 (2009) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7 as a key study;

ii. An *in vitro* mammalian chromosome aberration test according to the OECD TG 473 (1997) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7 as a supporting study.

4.2. Assessment of the information provided

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

4.2.1. Read-across adaptation rejected

111 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.

4.2.2. Source study not adequate for the information requirement

112 As explained in Section 0.1, under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 473.

113 Therefore, the following specifications must be met:

a) the maximum concentration tested induces 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration corresponds to 10 mM, 2 mg/mL or 2 µL/mL, whichever is the lowest;
b) data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures is reported;

114Both studies i. and ii. have been conducted according to the OECD TG 473.

115 However, the following specifications are not according to the requirements of the OECD TG 473:

116 Study i.:

a) the maximum tested concentration did not induce 55+5% of cytotoxicity compared to the negative control, and it did not induce the precipitation of the tested

substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL;

b) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures were not reported.
In the endpoint study record for study i., you report that the test doses used in the different experiments of the study were chosen based on cytoxicity and that the source substance was tested up to cytotoxic concentrations. These test concentrations range from 1.22 µg/ml to 78.12, and 156.25 µg/ml across the experiments.
However no detailed information on the cytotoxicity observed with the treated cultures in the different experiments is provided to justify the selection of the test concentrations.
In the absence of this information, it is not possible to confirm that the test concentrations used in study i. are appropriate to investigate the cytogenicity of the source substance according to the OECD TG 473.

117 Study ii:

b) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s), polypoloidy and endoreplication for the treated and control cultures were not reported.
In the endpoint study record provided in the technical dossier for study ii. you report that no structural chromosomal aberrations were observed in this study, but you indicate that an increase in polyploidy was detected in the presence and in the absence of metabolic activation. You conclude that "*whereas this study showed no indication of clastogenic properties, a polyploidy inducing effect cannot be excluded*".
However no detailed results on the frequency of cells with structural chromosomal aberrations, polyploidy and endoreplication are provided in the endpoint study record for study ii.
In the absence of this information it is not possible to assess the findings reported for this study and to critically evaluate your conclusions on these findings.

118 Based on the above, the information provided in studies i. and ii. does not cover the key specification(s) required by the OECD TG 473.

119 Therefore, the information requirement is not fulfilled.

120 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1.

121 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

4.3. Specification of the study design

To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

5. In vitro gene mutation study in mammalian cells

122 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

5.1. Triggering of the information requirement

123 Your dossier contains an adaptation for an *in vitro* gene mutation study in bacteria, and an adaptation for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study.

124 The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in requests 1 and 4.

125 The result of the requests for an *in vitro* gene mutation study in bacteria and for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

~~126~~ Consequently, you are required to provide information for this information requirement, if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

127 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1.

128 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

5.2. Information provided

129 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided an in vitro gene mutation study in mammalian cells (OECD TG 476) (2009) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7.

5.3. Assessment of the information provided

130 We have assessed this information and 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.

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

5.4. Specification of the study design

132 To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

6. Screening for reproductive/developmental toxicity

133 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1., if there is no

evidence from analogue substances, QSAR or *in vitro* methods that the substance may be a developmental toxicant.

6.1. Information provided

134 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) (1997) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7.

6.2. Assessment of the information provided

135 We have assessed this information and 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.

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

137 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1.

138 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

6.3. Specification of the study design

139 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

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

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

7. Short-term toxicity testing on fish

142 Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

7.1. Information provided

143 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided an OECD TG 203 study (1997) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7.

7.2. Assessment of the information provided

144 We have assessed this information and 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.

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

146 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1.

147 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

7.3. Study design and test specifications

148 OECD TG 203 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 2.

Reasons related to the information under Annex IX of REACH

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

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

8.1. Information provided

150 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 a weight of evidence approach based on the following lines of information:

i. A combined repeated dose and reproduction toxicity study with the analogue substance tetrahydromethylphthalic anhydride (MHTPA), EC 234-290-7 (1997);

ii. A 28-day repeated dose toxicity study with the analogue substance hexahydro-4 methylphthalic anhydride (4-MHHPA);

iii. A 90-d repeated dose toxicity study in rats (1969, [redacted] cited in the WHO Concise International Chemical Assessment Document 75) with the analogue substance trimellitic anhydride (TMA);

iv. A 90-d repeated dose toxicity study in dogs (1970, [redacted] cited in the WHO Concise International Chemical Assessment Document 75) with the analogue substance trimellitic anhydride (TMA).

151 You conclude from this information that "*Taken all data from MTHPA and structural analogue substances together, a new 90 day toxicity study with MTHPA is not required and not in line with concerns regarding animal welfare and the use of animals for experimental purposes. The data available for chemically almost identical substances in different species and for exposure periods of 90 days support the findings noted in OECD 422 study taking the time extrapolation factor into account. Therefore, the OECD 422 study is considered to represent a reliable basis for DNEL derivation for MTHPA*."

152 In your comments to the draft decision, you propose a new adaptation for this information requirement by using grouping and read-across from the source substance 4-MHHPA, and provided the following information:

153 Robust study summary of a OECD TG 408 study in rats conducted with 4-MHHPA.

8.2. Assessment of the information provided

154 We have assessed this information and identified the following issues.

Weight of evidence adaptation

155 As explained under Section 0.2, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

156 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Section 8.6.2 at Annex IX includes similar information that is produced by the OECD TG 408. The following aspects of systemic toxicity are covered: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity.

157 We have assessed the individual sources of information with regard to relevance and reliability and identified the following issue(s):

8.2.1. Aspect 1) In-life observations

158 In-life observations (aspect 1) must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

159 For the reasons explained in the section 0.2, the sources of information (ii.-iv.) that are lacking robust study summaries cannot be considered as contributing for this aspect with any relevant and reliable information. In addition, you have not established that these sources of information that are on analogue substances can predict the relevant property of the Substance.

160 The source of information i. provides relevant information on the above-mentioned in life observations, but has the following deficiencies affecting the reliability of its contribution to the weight of evidence adaptation.

161 Investigations/specifications in a sub-chronic toxicity study (OECD TG 408) include dosing of the Substance daily for a minimum of 90 days.

162 According to the information provided in your dossier, the study i. has an exposure duration of 49 days for males and 38 days for females.

163 This means that the exposure duration in study i. is shorter than the minimum exposure duration expected from a study conducted according to the OECD TG 408. This condition of exposure is essential because the effects observed over the required period of exposure of 90-days might be considerably more pronounced than over a shorter study duration.

164 Furthermore, for the reasons explained in the section 0.2 you have not established that the information on the analogue substance MTHPA (EC 234-290-7) can reliably contribute to the weight of evidence intended to identify the properties of the Substance.

165 Therefore, for all the reasons explained above, the reliability of the contribution of the results from the study i. to the weight of evidence with regard to aspect 1 is limited.

8.2.2. Aspect 2) blood chemistry

166 Information on blood chemistry (aspect 2) must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary).

167 For the reasons explained in the section 0.2, the sources of information (ii.-iv.) that are lacking robust study summaries cannot be considered as contributing for this aspect with any relevant and reliable information. In addition, you have not established that these sources of information that are on analogue substances can predict the relevant property of the Substance.

168 The source of information i. provides relevant information on some of the above-mentioned blood chemistry.

169 According to the OECD TG 408 paragraphs 34, serum total T4, T3 and TSH should be measured in the study. According to the information provided in your dossier, serum total T4, T3 and TSH were not measured in study i.

170 Furthermore, investigations/specifications in a sub-chronic toxicity study (OECD TG 408) include haematological and clinical biochemistry tests as specified in paragraphs 30-38 of the test guideline. According to the information provided in your dossier, the haematological and clinical biochemistry tests conducted as part of study i. were performed on males only.

171 This means that the results from study i. are not informing on the potential impact of exposure to the Substance on haematology and clinical biochemistry in females, as required by the OECD TG 408.

172 Furthermore, the issue on the exposure duration of study i. identified in section 8.2.1. above applies equally to aspect 2.

173 Finally, for the reasons explained in the section 0.2, you have not established that the information on the analogue substance MTHPA (EC 234-290-7) used in study i. can reliably contribute to the weight of evidence intended to identify the properties of the Substance.

174 Therefore, for the reasons presented above, source i. does not provide relevant information on some aspects of blood chemistry, and for the elements covered the reliability of the contribution of the results obtained from this study to the weight of evidence with regard to aspect 2 is limited.

8.2.3. Aspect 3) organ and tissue toxicity

175 Organ and tissue toxicity (aspect 3) must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale) and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

176 For the reasons explained in the section 0.2, the sources of information (ii.-iv.) that are lacking robust study summaries cannot be considered as contributing for this aspect with any relevant and reliable information. In addition, you have not established that these sources of information that are on analogue substances can predict the relevant property of the Substance.

177 The source of information i. provides relevant information on some of the above-mentioned organ and tissue toxicity.

178 Investigations/specifications in a sub-chronic toxicity study (OECD TG 408) include:

a. gross pathology as specified in paragraphs 43-46 of the test guideline;

b. full histopathology as specified in paragraphs 47-49 of the test guideline.

179 According to the information provided in your technical dossier, the following investigations/specifications are not to the requirements of the OECD TG 408 in study i.:

a. data on gross pathology findings are missing. According to the information reported in the robust study summary for the provided study, gross pathology investigations on the prostate and seminal vesicles for all males are missing.

b. data on histopathology findings are missing. According to the information reported in the robust study summary for the provided study, histopathology in the following organs of all the control and high dose animals are missing: spinal chord, lymph nodes, peripheral nerve (sciatic or tibial), skeletal muscle. Furthermore,

information on histopathology in the testis, epididymides, prostate and seminal vesicles with coagulating glands in fertile animals is also missing from the provided study.

180 Furthermore, the issue on the exposure duration of study i. identified in section 8.2.1 above applies equally to aspect 3.

181 Finally, for the reasons explained in the section 0.2, you have not established that the information on the analogue substance MTHPA (EC 234-290-7) used in study i. can reliably contribute to the weight of evidence intended to identify the properties of the Substance.

182 Therefore, for the reasons presented above, source i. does not provide relevant information on some aspects of organ and tissue toxicity, and for the elements covered the reliability of the contribution of the results obtained from this study to the weight of evidence with regard to aspect 3 is limited.

8.3. Conclusion on the weight of evidence

183 Taken together, there is only one source as indicated above, that provides information on aspect 1 (in-life observations). However, for aspect 2 (blood chemistry) and aspect 3 (organ and tissue toxicity), this source of information provides relevant information only on some elements of these aspects, and does not cover the entire set of elements on haematology, clinical biochemistry, gross pathology and full histopathology expected to be obtained from the OECD TG 408.

184 Furthermore, any robust conclusion on any of the 3 aspects that are covered is hampered by the shorter exposure duration and the deficiencies by the use of information on an analogue substance in study i.

185 This increases the uncertainty of the results in such a way that prevents reaching a conclusion on any of these aspects.

186 Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 408 study.

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

188 In your comments to the draft decision you propose a new adaptation for this information requirement by using grouping and read-across from the source substance 4-MHHPA. The information you provided addresses the deficiencies identified, as explained in Section 0.1.

189 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

8.4. Specification of the study design

190 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.

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

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

9. Pre-natal developmental toxicity study in one species

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

9.1. Information provided

194 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 lines of information:

i. A combined repeated dose and reproduction toxicity study with the analogue substance tetrahydromethylphthalic anhydride (MHTPA), EC 234-290-7 (1997).

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).

195 You conclude from this information that "*the available data for structural homologues of MTHPA indicate neither potential for teratogenic effects nor for reproduction toxicity in different species. These data, together with the available information on MTHPA, allow a scientific validated evaluation of the respective endpoints and further tests would not be in line with concerns regarding animal welfare and the use of animals for experimental purposes*".

196 In your comments to the draft decision you propose a new adaptation for this information requirement by using grouping and read-across from the source substance 4-MHHPA, and provided the following information:

Robust study summary of a OECD TG 414 study in rats conducted with 4-MHHPA.

9.2. Assessment of the information provided

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

Weight of evidence

198 As explained under Section 0.2, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

199 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes similar information that is produced by the OECD TG 414. The following aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

200 We have assessed the individual sources of information with regard to relevance and and reliability and identified the following issue(s):

9.2.1. Aspect 1) Pre-natal developmental toxicity

Prenatal developmental toxicity includes information after prenatal exposure on embryonic/foetal survival (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).

201 For the reasons explained in the section 0.2, the sources of information (ii.-vi.) that are lacking robust study summaries cannot be considered as contributing for this aspect with any relevant and reliable information. In addition, you have not established that these sources of information that are on analogue substances can predict the relevant property of the Substance.

202 The source of information i. provides relevant information on some of the above-mentioned parameters on prenatal developmental toxicity.

203 Investigations/specifications in a pre-natal developmental toxicity study (OECD TG 414) include that the foetuses are examined for sex and body weight/external, skeletal and soft tissue alterations (variations and malformations)/number of resorptions and or live foetuses/ measurement of anogenital distance in live rodent foetuses.

204 According to the information on the source of information i. provided in your dossier, the number of resorptions, post-implantation losses and live fetuses were counted. The foetuses were examined for sex and body weight and external alterations.

205 However they were not examined for skeletal and soft tissue alterations (variations and malformations).

206 Furthermore, the source of information i. has the following deficiency affecting the reliability of its contribution to the weight of evidence adaptation.

207 Investigations/specifications in a pre-natal developmental toxicity study (OECD TG 414) include that at least 20 female animals with implantation sites are included for each test and control group.

208 According to the information provided in your technical dossier, the following investigations/specifications are not to the requirements of the OECD TG 414 in study i. since only 12 female animals were included in the study for each test and control group.

209 Based on the information provided in the dossier, the study i. does not inform on structural malformations and variations (visceral and skeletal).

210 While the study i. does inform on embryonic/foetal survival (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size), the information on these elements of aspect 1 obtained from study i. has a lower statistical power than expected from a study conducted according to the OECD TG 414 since the study provided has only 12 animals in each group.

211 Furthermore, for the reasons explained in the section 0.2, you have not established that the information on the analogue substance MTHPA (EC 234-290-7) used in study i. can reliably contribute to the weight of evidence intended to identify the properties of the Substance.

212 Therefore, for the reasons presented above, source i. does not provide relevant information on some aspects of pre-natal developmental toxicity, and for the elements covered the contribution of the results obtained from this study to the weight of evidence with regard to aspect 1 is limited. The lower statistical power of the study introduces uncertainty in the results, which must be considered in the assessment of the weight of the information from this study.

9.2.2. Aspect 2) Maternal toxicity

213 Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

214 For the reasons explained in the section 0.2, the sources of information (ii.-vi.) that are lacking robust study summaries cannot be considered as contributing for this aspect with any relevant and reliable information. In addition, you have not established that these sources of information that are on analogue substances can predict the relevant property of the Substance.

215 The source of information i. provides relevant information on the above-mentioned parameters on maternal toxicity. However, the deficiencies on the statistical power of the results obtained from study i. identified for aspect 1) in section 9.2.1 above equally apply to aspect 2.

216 Furthermore, for the reasons explained in the section 0.2, you have not established that the information on the analogue substance MTHPA (EC 234-290-7) used in study i. can reliably contribute to the weight of evidence intended to identify the properties of the Substance.

217 Therefore, the reliability of the contribution of the results obtained from this study to the weight of evidence with regard to aspect 2 is limited.

9.2.3. Aspect 3) Maintenance of pregnancy

218 Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

219 For the reasons explained in the section 0.2, the sources of information (ii.-vi.) that are lacking robust study summaries cannot be considered as contributing for this aspect with any relevant and reliable information. In addition, you have not established that these sources of information that are on analogue substances can predict the relevant property of the Substance.

220 The source of information i. provides relevant information on the above-mentioned parameters on maintenance of pregnancy. However, the deficiencies on the statistical power of the results obtained from study i. identified for aspect 1) in section 9.2.1 above equally apply to aspect 3.

221 Furthermore, for the reasons explained in the section 0.2, you have not established that the information on the analogue substance MTHPA (EC 234-290-7) used in study i. can reliably contribute to the weight of evidence intended to identify the properties of the Substance.

222 Therefore, the reliability of the contribution of the results obtained from this study to the weight of evidence with regard to aspect 3 is limited.

9.3. Conclusion on the weight of evidence

223 Taken together, there is only one source of information as indicated above that provides information on aspects 2 (maternal toxicity) and 3 (maintenance of pregnancy).

224 However, for aspect 1 (pre-natal developmental toxicity), it provides relevant information only on some elements of this aspect, and does not cover the elements on structural malformations and variations (visceral and skeletal) expected to be obtained from the OECD TG 414.

225 Furthermore, any robust conclusion on any of the 3 aspects that are covered is hampered by reduced statistical power of the results as a consequence of the low number of animals used and by the deficiencies of use of information on an analogue substance in study i.

226 This increases the uncertainty of the results in such a way that prevents reaching a conclusion on any of these aspects.

227 Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 414 study.

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

229 In your comments to the draft decision you propose a new adaptation for this information requirement by using grouping and read-across from the source substance 4-MHHPA. The information you provided addresses the deficiencies identified, as explained in Section 0.1.

230 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

9.4. Study design and test specifications

231 A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[2] administration of the Substance.

10. Long-term toxicity testing on aquatic invertebrates

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

10.1. Information provided

233 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided the following information with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7:

(i) an OECD TG 211 study (2010);

(ii) an OECD TG 211 study (1997).

10.2. Assessment of the information provided

[2] Guidance on IRs and CSA, R.7a, Section R.7.6.2.3.2.

234 We have assessed this information and 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.

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

236 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1.

237 However, as the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

238

10.3. Study design and test specifications

239 OECD TG 211 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 2.

11. Long-term toxicity testing on fish

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

11.1. Information provided

241 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided an

(i) OECD TG 204 study (1997) with the analogue substance tetrahydromethylphthalic anhydride (MTHPA), EC number 234-290-7.

242 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.

243 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).

11.2. Assessment of the information provided

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

11.2.1. Read-across adaptation rejected

245 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.

11.2.2. Source study not adequate for the information requirement

246 As explained in Section 0.1, 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.

247 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.

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

249 This study 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.

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

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

252 In your comments to the draft decision, you have recognised the deficiencies noted for your grouping of substances and read-across approach (Annex XI, Section 1.5.). 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.

11.2.3. Weight-of-evidence adaptation

253 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.

254 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.

255 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.

256 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.

257 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.

258 We have assessed the individual source of information in regard to relevance and reliability and identified the following issues:

Key parameters 1, 3-4

259 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.

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

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

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

263 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.

264 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*".

265 The Substance has the following properties related to the estimation of applicability domain:

- hydrolysed diacid form of the Substance ionise at environmentally relevant pHs, since in the dossier you report pKa1= 3.82 and pKa2= 6.85 at 20 deg C;
- Hydrolysed diacid form of the Substance is reactive since in the "*Read-across justification report for 3-MTHPA D4 (CAS 5333-84-6; EC 226-247-6)*" 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).

266 Due to the rapid hydrolysis of the Substance (as indicated in section 2.3 of this decision), 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.

267 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.

268 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

269 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).

270 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.

271 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.

272 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.

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

11.3. Study design and test specifications

274 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.).

275 OECD TG 210 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 2.

12. Simulation testing on ultimate degradation in surface water

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

12.1. Information provided

277 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.2.1.2. and 9.2.1.4 To support the adaptation, you have provided the following justifications:

(i) *"the study does not need to be conducted because the substance is readily biodegradable"*;
(ii) "*In accordance with REACH Regulation 1907/2006/EC (Annex IX - 9.2.1.2 & 9.2.1.4 - column 2) simulation tests of biodegradation in water and sediment do not need to be conducted because direct and indirect exposure of sediment is unlikely.*".

12.2. Assessment of information provided

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

12.2.1. The Substance is not readily biodegradable

279 Under Section 9.2.3., Column 2 of Annex IX to REACH, this information may be omitted if the substance is readily biodegradable.

280 The following criteria is regarded as evidence of ready biodegradability:

- The pass level for ready biodegradability (i.e. 60% degradation) is reached within 28 days in an OECD TG 301C study.

281 Furthermore, for QSAR predictions done with BIOWIN models, a substance is predicted as readily biodegradable if both these criteria are met

- Biowin3 result is ≥ 2.75 and Biowin5 result is ≥ 0.5 (EpiSuite BIOWIN version 4.10 helpfile).

282 Your justification (i) to omit this information Under Section 9.2.3., Column 2 of Annex IX refers to the Substance being readily biodegrable.

283 Your dossier provides the following information on ready biodegradability:

(i) two OECD TG 301C studies with analogue substances showing no ready biodegrability (0% degradation (O_2 consumption) after 28 days);
(ii) QSAR results with BIOWIN 4.10 for the Substance estimating no ready biodegrability (Biowin3 result is 2.83 and Biowin5 result is 0.29). In addition, based on the results of Biowin2, Biowin3 and Biowin6, you conclude that the Substance "*was estimated as being inherently biodegradable*".

284 Based on the above, there is no evidence in your dossier that the Substance is readily biodegradable because in the two studies the pass level is not reached in 28 days and the QSAR results show no ready biodegradability.

285 Concequently, your adaptation is rejected.

12.2.2. Your justification (ii) 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..

286 Your justification (ii) to omit this information refers to unlikely exposure of the sediment compartment (Column 2, Annex IX, Section 9.2.1.4), which is not a specific rule for adaptation for simulation testing on ultimate degradation on surface water under Column 2, Annex IX, Section 9.2.1.2..

287 In addition, your justification (ii) 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.

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

12.3. Study design and test specifications

289 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.

290 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.).

291 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.

292 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.

293 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.

294 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.

295 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.).

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).

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

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]

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[3].

(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[4].

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