~~Confidential~~

Helsinki, 01 December 2022

Addressees
Registrant(s) of JS_34090-76-1 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
25 October 2010

Registered substance subject to this decision ("the Substance")
Substance name: Tetrahydro-4-methylphthalic anhydride
EC number: 251-823-9

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit information under request 8 below by ***10 March 2025*** and all other information listed below by ***6 August 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. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested below (Annex VIII, Section 8.6.1.);

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;

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

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

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

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

Information required depends on your tonnage band

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

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

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

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

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

Appendix 1: Reasons for the decision

Contents

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.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- 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 predict the properties of the Substance from information obtained from the source substance tetrahydromethylphthalic anhydride (MTHPA), EC 234-290-7.

11 You provide the following reasoning for the prediction of ecotoxicological properties in the in the executive summary of IUCLID Section 6.1: "Aquatic toxicity studies have been undertaken on a structural analogue of the substance, MTHPA".

12 Similarly, you flag the information provided on the analogue substance MTHPA in relation with the toxicological information requirements listed above as "read-across from supporting substance (structural analogue or surrogate)" in your technical dossier.

13 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.

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

0.1.1.1. Absence of read-across documentation

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

16 You have provided robust study summaries for studies conducted with another substance, MTHPA, EC 234-290-7, than the Substance in order to comply with the REACH information requirements.

17 However, you have not provided documentation as to why this information is relevant for the Substance and thus why the properties of the Substance may be predicted from information on the source substance(s).

18 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance.

19 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.

20 You argue that read across *"from 4-MHHPA (EC No 243-072-0) to MTHPA generic is justified, and thus also to the Substance (4-MTHPA). 4-MHHPA, MTHPA and the Substance are expected to have similar (eco)toxicological properties."*

21 To support your claim, you have provided robust study summaries of the available studies on the source substance MTHPA (OECD TG 422) and on the source substance 4-MHHPA (OECD TG 407, 408, 421 and 414) which support that MTHPA and 4-MHHPA have quantitatively and qualitatively similar effects.

22 The Substance (4-MHTPA) is a monoconstituent substance consisting of one of the three isomers which make up MHTPA generic.

23 To support the read-across between 4-MHTPA generic and the Substance (4-MTHPA), you have provided QSAR profiling of the isomers present in the Substance (4-MTHPA) and MTHPA generic. This information indicates that the other constituents (isomers) of the source substance MTHPA generic, mainly 3-MTHPA, are likely to have similar toxicity properties as the Substance (4-MTHPA).

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

25 Furthermore, ECHA considers that the compositional similarities between MTHPA generic and the Substance (4-MTHPA) together with the QSAR profiling of the isomers present in the substances constitute an adequate basis to predict the properties of the Substance from MTHPA generic and thus also from 4-MHHPA.

0.1.1.2. Adequacy and reliability of source studies

26 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.

27 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, 6 and 11. Therefore, no reliable predictions can be made for these information requirements.

28 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.

29 For sub-acute toxicity (request 6), you have also provided in your comments a new robust study summary of an OECD TG 407 study and an OECD TG 408 study with the source substance 4-MHHPA, which makes the current issue of adequacy and reliability of source study, for request 6, no longer relevant.

0.1.2. Conclusion on the read-across approach

30 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.

31 As described above, the new 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 0.1.1.2 for the request 11). However, as the information is currently not available in the registration dossier, the deficiencies remain in the decision.

32 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

33 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.);
- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.).

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

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

36 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

37 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.

38 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.

39 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.

40 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.

41 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 new 90 day toxicity study with MTHPA is not required and not in line with animal welfare ideas. 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"*.
- 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 of the OECD 422 study allow a scientific validated evaluation of the respective endpoints and further tests would not be in line with animal welfare ideas*".

42 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

43 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.

44 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)).

45 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.

46 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]

47 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.

48 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.

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

50 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.

51 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

52 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.

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

54 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.

55 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).

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

57 In your justifications for the weight of evidence adaptations and in the respective sections of your Chemical Safety Report, 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".

58 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.

59 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

60 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.).

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

62 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).

63 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.

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

65 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

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

information on analogue substances, as specified in the endpoint specific sections of this document.

66 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.

67 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.

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

69 Therefore, the information from the analogue substances cannot reliably contribute to your weight of evidence adaptations.

70 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

71 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.

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

73 However, for the information requirement Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) the identified issues remain because you have not addressed this information requirement in your comments.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

74 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

75 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

76 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.

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

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

79 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

80 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

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

2.1. Information provided

82 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

83 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.

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

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

86 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

87 The Substance is difficult to test since it is hydrolytically unstable (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). 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.

88 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.

89 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.

90 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

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

3.1. Information provided

92 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

93 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.

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

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

96 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

97 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. 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

98 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

99 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

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

4.2.1. Read-across adaptation rejected

101 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.

102 In addition, ECHA identified endpoint specific issue(s) addressed below.

4.2.2. Source study not adequate for the information requirement

103 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.

104 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;

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

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

107 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.

108 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.

109 The information provided in studies i. and ii. does not cover the key specification(s) required by the OECD TG 473.

110 Therefore, the information requirement is not fulfilled.

111 In your comments to the draft decision, the information you provided addresses the deficiencies identified, as explained in Section 0.1. Furthermore, you have provided robust study summaries with the information that addresses the deficiencies identified under "4.2.2 Source study not adequate for the information requirement" above.

112 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

113 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

114 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

115 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.

116 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.

117 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.

~~118~~ 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.

5.2. Information provided

119 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

120 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.

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

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

123 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.

5.4. Specification of the study design

124 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. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days)

125 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

6.1. Information provided

126 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.

127 In your comments to the draft decision, you have provided provided read-across justifications and a robust study summary of an OECD TG 407 study and an OECD TG 408 study in rats conducted with the source Substance 4-MHHPA (EC No. 243-072-0).

6.2. Assessment of the information provided

6.2.1. Read-across adaptation rejected

128 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.

129 In addition, ECHA identified endpoint specific issue(s) addressed below.

6.2.2. Source study not adequate for the information requirement

130 As explained in section 0.1, 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 407.

131 Therefore, the following specifications must be met:

a. clinical biochemistry tests as specified in paragraphs 34-39 of the test guideline;
b. gross pathology, including incidence and severity, as specified in paragraphs 40-46 of the test guideline.
c. full histopathology, including incidence and severity, as specified in paragraphs 47-49 of the test guideline.

132 The provided study is described as a combined repeated dose toxicity study with the reproduction / developmental toxicity screening test.

133 However, the following specifications are not according to the requirements of the OECD TG 407:

a. data on clinical biochemistry findings are missing. The OECD TG 407 requires that clinical biochemistry "should be performed on blood samples obtained of <u>all animals</u> just prior to or as part of the procedure for euthanasia of the animals" (OECD TG 407, paragraph 34). According to the information reported in the robust study summary for the provided study, clinical biochemistry was investigated in males only. Investigations on clinical biochemistry in females are missing from this study.
b. 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.

c. 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.

134 Therefore, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) of the corresponding OECD TG.

135 On this basis, your adaptation is rejected and the information requirement is not fulfilled.

136 In your comments to the draft decision, you provide a robust study summary of a OECD TG 407 study and a OECD TG 408 study conducted with the source substance 4-MHHPA, which addresses the current information requirement, as explained in Section 0.1..

137 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

138 Annex VIII, Section 8.6.1., Column 2 provides that an experimental study for this information requirement is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

139 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 8). According to Annex VIII, Section 8.6.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not therefore need to be conducted.

140 Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

7. Short-term toxicity testing on fish

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

7.1. Information provided

142 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

143 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.

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

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

146 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

147 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)

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

8.1. Information provided

149 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);

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

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

iii. A scientific publication on Biochemical effects and monitoring of exposure of rats to vapours of the analogue substance 4-methylcyclohexyl-1,6-dicarboxylic acid anhydride (HHPA) (1986, Savolainen H);

iv. 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);

v. 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);

vi. 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 these data together, a new 90 day toxicity study with MTHPA is not required and not in line with animal welfare ideas. 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 have provided provided read-across justifications and a robust study summary of an OECD TG 408 study in rats conducted with the source Substance 4-MHHPA (EC No. 243-072-0).

8.2. Assessment of the information provided

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

154 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.

155 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.

156 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

157 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).

158 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.

159 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.

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

161 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.

162 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.

163 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.

164 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

165 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).

166 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.

167 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.

171 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.

172 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.

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

174 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.

175 Therefore, for the reasons presented above, the study 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

176 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).

177 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.

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

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

180 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.

181 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.

c. 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.

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

183 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.

184 Therefore, for the reasons presented above, the study 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

185 Taken together, there is only one source as indicated above, that provides information on aspect 1 (in-life observations).

186 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 this aspect, 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.

187 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.

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

189 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.

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

191 In your comments to the draft decision, you provide a robust study summary of a OECD TG 408 study, conducted with the source substance 4-MHHPA, which adressed the current information requirement, as explained in Section 0.1..

192 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

193 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.

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

195 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

196 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

197 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).

198 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).

199 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 of the OECD 422 study allow a scientific validated evaluation of the respective endpoints and further tests would not be in line with animal welfare ideas".

200 In your comments to the draft decision, you have provided provided read-across justifications and a robust study summary of an OECD TG 414 study in rats conducted with the source Substance 4-MHHPA (EC No. 243-072-0).

9.2. Assessment of the information provided

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

202 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.

203 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.

204 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

205 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).

206 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. I

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

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

209 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.

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

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

212 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.

213 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.

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

215 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.

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, 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

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

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.

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

221 The source of information i. provides relevant information on the above-mentioned parameters on maternal toxicity.

222 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.

223 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.

224 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

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.

225 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.

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

227 The source of information i. provides relevant information on the above-mentioned parameters on maintenance of pregnancy.

228 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.

229 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.

230 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

231 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). 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.

232 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.

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

234 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.

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

236 In your comments to the draft decision, you provide a robust study summary of a OECD TG 414 study, conducted with the source substance 4-MHHPA, which addresses the current information requirement, 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.

9.4. Study design and test specifications

238 A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[5] administration of the Substance.

10. Long-term toxicity testing on aquatic invertebrates

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

10.1. Information provided

240 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

241 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.

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

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

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

244 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.

10.3. Study design and test specifications

245 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.

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

11. Long-term toxicity testing on fish

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

11.1. Information provided

248 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.

249 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.

250 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

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

11.2.1. Read-across adaptation rejected

252 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.

253 In addition, ECHA identified endpoint specific issue(s) addressed below.

11.2.2. Source study not adequate for the information requirement

254 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.

255 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.

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

257 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.

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

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

260 In your comments on 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

261 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.

262 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.

263 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.

264 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.

265 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.

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

Key parameters 1, 3-4

267 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.

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

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

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

271 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.

272 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*".

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

- hydrolysed diacid form of the Substance ionises at environmentally relevant pHs, since in the dossier you report pKa1 = 4.20 and pKa2 = 6.35 at 20°C;
- hydrolysed diacid form of the Substance is reactive since in the [redacted]" 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).

274 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.

275 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.

276 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

277 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).

278 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.

279 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.

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

11.3. Study design and test specifications

280 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.).

281 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

282 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

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

(i) "*In accordance with REACH Regulation 1907/2006, Annex IX, Column 2 simulation testing on biodegradation in water and sediment (required in Sections 9.2.1.2 and 9.2.1.4) does not need to be conducted as direct or indirect exposure of the aquatic and terrestrial compartments for this substance are unlikely. The substance is hydrolysed rapidly in a few minutes to the corresponding dicarboxylic acid. In addition based on the intended uses, exposure of sediments is not likely.*"

284 Furthermore, you have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(ii) Half life in water: 360 hours, calculated using a fugacity model (Mackay, Level III) in EPIWIN (v.4.0).

12.2. Assessment of information provided

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

12.2.1. Your justification to omit the study (i) does not refer to any adaptation possibility

286 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..

287 Your justification (i) to omit this information refers to unlikely exposure of the aquatic and sediment compartment (Column 2, Annex IX, Section 9.2.1.4) and to rapid hydrolysis, which are not specific rules for adaptation for simulation testing on ultimate degradation in surface water under Column 2, Annex IX, Section 9.2.1.2.. In addition, your justification (i) does not refer to any legal ground for adaptation under Annex XI to REACH.

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

12.2.1.1. Assessment of (Q)SAR prediction (ii)

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

i. the prediction needs to be derived from a scientifically valid model,

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

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

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

290 With regard to these conditions, we have identified the following issue:

Lack of documentation for the prediction (QMRF and QPRF)

291 Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and Guidance on IRs and CSA, Section R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) and a (Q)SAR Prediction Reporting Format document (QPRF).

292 A QMRF must report, among others, the following information:

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

293 A QPRF must report, among others, the following information:

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

294 You have not provided a QMRF and a QPRF with the above information. Rather, you have only provided the final result from the software model included in EPIWIN.

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

296 Based on the above, your adaptation is rejected.

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

12.3. Study design and test specifications

298 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.

299 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.).

300 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.

301 As specified in Guidance on IRs and CSA, Section R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test material concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance.

302 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.

303 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.).

13. Identification of degradation products

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

13.1.1. You have provided no information

305 You have provided information on the identity of the hydrolysis products, but no information on the identity of further transformation/biodegradation products for the Substance, which is required for this information requirement.

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

13.2. Study design and test specifications

307 Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible.

308 In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You must obtain this information from the degradation study requested in Request 12 .

309 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Request 12) must be conducted at 12°C and at a test concentration < 100 µg/L.

310 However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, e.g. 20°C) and at higher application rate (i.e. > 100 µg/L).

Reasons related to the information under Annex X of REACH

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

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

14.1. Information provided

312 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, and you have provided sources of information as described under section 4.1 above.

14.2. Assessment of the information provided

313 As explained under section 0.1, 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.

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

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

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

317 3) Maintenance of pregnancy: Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure.

318 We have assessed the information provided, which is the same as for the prenatal developmental toxicity in the first species. For the same reasons as already presented in sections 9.2 and 9.3 above it is not possible to conclude whether the Substance has or has not hazardous properties in relation to PNDT in the second species. T

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

320 In the comments on the draft decision you do not comment on this request, i.e. information requirement of Annex X, Section 8.7.2; i.e. pre-natal developmental toxicity study in a second species.

321 The previously identified issues remain.

14.3. Specification of the study design

322 A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study (request 9 in this decision).

References

The following documents may have been cited in the decision.

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

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

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

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

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

Appendix 2: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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).

In your comments to the draft dection, you requested additional time to conduct the environmental fate and hazard studies. You propose to extend the deadline to 41 months. You cite complexity of the testing and laboratory capacity as reasons for the extension.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. Based on the documentary evidence provided, ECHA has agreed with your request for a deadline extension and has extended the deadline to 41 months.

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

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

Appendix 3: Addressees of this decision and their corresponding information requirements

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

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

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

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[6].

(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[7].

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