~~Confidential~~

Helsinki, 25 October 2022

Addressees
Registrant(s) of JS_85-43-8 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
24/09/2010

Registered substance subject to this decision ("the Substance")
Substance name: 1,2,3,6-tetrahydrophthalic anhydride
EC number: 201-605-4

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 2 below by ***30 January 2025*** and all other information listed below by ***30 January 2026***.

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

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

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490).

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

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

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

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

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

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

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

1 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 in a second species (Annex X, Section 8.7.2.).

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

3 You have provided justifications for using information on analogue substances in separate endpoint study records under sections 7.5.1 and 7.8.2 in IUCLID and in the respective sections of your Chemical Safety Report.

4 In your justifications you explain that "THPA 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.".

5 The details of the identity of the analogue substances and of the set of information provided for each of the information requirements listed above are provided in the endpoint-specific sections of this document.

6 ECHA understands that your justification for using information on analogue substances in your weight of evidence approach is based on the assumption that the structurally similar substances cause the same type of effect(s).

7 You consider that the information that you have provided on the Substance itself and on the analogue substances, when taken together, are adequate to fulfil the information requirements under consideration.

8 Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Section, before assessing the specific standard information requirements in the following Sections.

9 Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

10 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 that the Substance has or has not the (dangerous) property investigated by the required study.

11 Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence adaptation.

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

- For the information requirement for a sub-chronic (90-day) toxicity study: "*Considering all of these data together, a 90 day toxicity study with THPA 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 of the shorter duration OECD 407 study taking the time extrapolation factor into account. Therefore, the OECD 407 study is considered to represent a reliable basis for DNEL derivation for THPA*";

- For the information requirements for pre-natal developmental toxicity studies: "*The available data for structural homologues of THPA indicate neither potential for teratogenic effects nor for reproduction toxicity in different species. These data, together with the available information of the OECD 421 study, are sufficient to permit evaluation of the respective endpoints and further tests would not be in line with current concerns regarding animal welfare and the use of animals in scientific experiments*".

13 However, your justifications do not include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous properties investigated by the required studies.

14 In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptations. Your weight of evidence approaches have deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Sections below.

15 These issues identified below are essential for the information requirements of Sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.) and Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in which you invoked a weight of evidence.

0.1.1. Documentation of the lines of information used in your weigh to evidence adaptations.

16 Annex XI, Section 1.2 requires that whenever weight of evidence is used adequate and reliable documentation must be provided. Such documentation must explain how the information from several independent sources together enable, 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. The justification must have regard to the information that would otherwise be obtained from the study that shall normally be performed for this information requirement.

17 In all cases, the information provided shall be adequate for the purpose of classification, labelling and/or risk assessment, and adequate and reliable documentation shall be provided, including:

— robust study summaries of the studies used as sources of information;

— a justification explaining why the sources of information together provide a conclusion on the information requirement.

18 In your justifications of your adaptations you provide short descriptions of information on the Substance and on analogue substances that you include in your weight of evidence approaches. These high level summaries confirm that these studies provide information which is relevant for the respective information requirements under consideration.

19 However, you have not provided individual endpoint study records for each of these studies. The description of some of these studies in the WHO CICAD report 75 included in your technical dossier do not provide more information than what is included in your justifications.

20 Furthermore, you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of these studies in the form of individual study records in your dossier.

21 Therefore, the information provided is not adequate for the purpose of classification, labelling and/or risk assessment.

22 In the absence of such information, ECHA considers that the studies which are only mentioned in your justifications of your adaptations cannot reliably contribute to your weight of evidence adaptations.

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

23 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.

24 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group).

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

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

27 You provide the following reasoning for the predictions of toxicological properties in the endpoint study record provided for this adaptation: "THPA 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."

28 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.

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

29 ECHA notes the following shortcomings with regards to the reliability of the contribution of the information of the analogue substances to your weight of evidence adaptations.

0.1.2.1. Missing supporting information

30 Annex XI, Section 1.5 of the REACH Regulation states that "physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)". For this purpose "it is important to provide supporting information to strengthen the rationale for the read-across" (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

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

32 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 bridging studies of comparable design and duration for the Substance and of the source substance(s).

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

34 Your read-across hypothesis assumes that the carboxylic acid anhydride group is the driver for the toxicological properties of these substances. As indicated above, the short narratives describing the studies included in the endpoint study records provided for your adaptations do not allow for an independent assessment of the reliability of these studies.

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

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

0.1.3. Information provided in your comments on the draft decision

37 In the comments to the draft decision you acknowledge the findings listed by ECHA in the draft decision. You refer to the weight of evidence/read-across approaches based on structural analogues of the Substance developed by the "US EPA in a hazard characterization document on a cyclic anhydrides category and the WHO grouping of cyclic anhydrides in their Concise International Chemical Assessment Document 75". You reiterate your views that such an approach "is applicable and justifiable, subject to the availability of data from studies meeting the standards stipulated by the relevant test guideline" and indicate that new information has become available for the endpoints under consideration and meeting the relevant test guidelines. You are of the opinion that "the identified data gap(s) can be reliably addressed by adaptation(s) permitted under Annex XI of the REACH Regulation aligned to current standards".

38 ECHA understands from your comments that you intend to revise your adaptations for the information requirements under consideration using information on structural analogues of the Substance either in a read-across or in a weight of evidence approach.

39 As this revised adaptation is not yet developed and submitted to ECHA, no conclusion on the compliance can currently be made.

40 You remain responsible for complying with this decision by the set deadline.

Reasons related to the information under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells

41 An in vitro gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (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.

42 Your dossier contains negative results for both an Ames test and an in vitro cytogenicity study. Therefore, the information requirement is triggered.

1.1. Information provided

43 You have provided an in vitro mammalian cell gene mutation test (2010) according to the OECD TG 476 with the Substance.

1.2. Assessment of the information provided

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

45 To fulfil the information requirement, the study must meet the requirements of OECD TG 476 or OECD TG 490 (Guidance on IRs and CSA, Table.7.7-2). The study you have submitted has been conducted using mouse lymphoma L5178Y cells as a test model and using the TK locus. This assay was originally described in the OECD TG 476 before a dedicated OECD TG was subsequently developed: the OECD TG 490. Paragraphs 62 to 64 of the OECD TG 490 (version adopted on 29 July 2016) provide specific recommendations for the interpretation of the biological significance of the test results obtained from an Mouse Lymphoma Assay (MLA) as described in the OECD TG 490. The basis of this interpretation method is a comparison of the increase in mutant frequency above the concurrent background observed in the test against the Global Evaluation Factor (GEF) for the applicable version of the MLA.

46 According to the information provided in your technical dossier, you consider that the statistically significant increase in mutant frequency detected at concentrations of 633 and 760 mg/ml in the presence of metabolic activation in experiment 1 was within the historical control range from the test laboratory. You also indicate that the increased mutant frequency was below the GEF. On that basis you concluded that "the observed increases were considered not related to the action of the test item and to be of no biological significance". No statistically significant increases in mutant frequency were observed in the second experiment.

47 The GEF for the microwell version of the MLA is specified in the OECD TG 490. However, the robust study summary provided in your dossier for the study does not include data on the cytotoxicity and the mutation frequency for the treated and control cultures as required by the OECD TG 490. In the absence of this information it is not possible to verify your assessment of the biological relevance of the increased mutant frequency observed in the experiment 1 and to assess your conclusion that these effects were not related to the test item.

48 Therefore, information provided does not cover the key parameters required by the OECD TG 490 and does not fulfil the information requirement.

1.3. Information provided in your comments on the draft decision

49 In your comments on the draft decision you agree with ECHA's statement that the robust study summary does not contain tabulated data on effects, the provided information being limited to a text summary of the salient findings. You attached tabular results providing

information on the cytotoxicity and the mutation frequency for the treated and control cultures for each of the test conditions of the study. You consider that this information addresses the limitations of the robust study summary of the existing study identified by ECHA and that the provision of a new study is not warranted.

50 ECHA has assessed the information against the requirement in the OECD TG 490. The information you have provided in your comments addresses the incompliances identified in this decision for this information requirement. However, as the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

1.4. Study design and test specifications

51 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.

Reasons related to the information under Annex IX of REACH

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

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

2.1. Information provided

53 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 experimental data:

i. Repeated dose toxicity: oral sub-acute study (2010, [redacted] according to the OECD TG 407 with the Substance.

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

ii. 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, cited in the WHO Concise International Chemical Assessment Document 75)

iii. Combined repeated dose and reproduction toxicity study with the analogue substance tetrahydromethylphthalic anhydride (MTHPA);

iv. 90-d repeated dose toxicity study in rats (1969, Hill Top Research cited in the WHO Concise International Chemical Assessment Document 75) with the analogue substance trimellitic anhydride (TMA);

v. 90-d repeated dose toxicity study in rats (1970, IBT cited in the WHO Concise International Chemical Assessment Document 75) with the analogue substance trimellitic anhydride (TMA);

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

55 You conclude from this information that "Considering all of these data together, a 90 day toxicity study with THPA 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 of the shorter duration OECD 407 study taking the time extrapolation factor into account.

56 Therefore, the OECD 407 study is considered to represent a reliable basis for DNEL derivation for THPA."

2.2. Assessment of the information provided

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

58 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.

59 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.

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

2.2.1. Aspects 1) to 3)

61 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).

62 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).

63 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).

64 The source(s) of information i. to vi. provide relevant information on the above-mentioned in life observations, but have the following deficiencies affecting the reliability of their contribution to the weight of evidence adaptation.

2.2.1.1. Reliability of the contribution of the studies ii. to vi.

65 The reliability of sources of information ii. to vi. is significantly affected by the deficiencies identified and explained under section 0.1.

66 Therefore, ECHA considers that the studies ii. to vi. cannot reliably contribute to your weight of evidence adaptation.

2.2.1.2. Reliability of the contribution of study i.

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

a. At least 10 male and 10 female animals for each test and control group.

b. Dosing of the Substance daily for a minimum of 90 days.

68 In study i., the following investigations/specifications are not to the requirements of OECD TG 408:

a. Only 5 males and 5 females were used in each test and control group.

b. An exposure duration of 28 days, i.e. less than the minimum of 90 days.

69 Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The lower statistical power and shorter exposure duration of the study introduce uncertainty in the results which must be considered. This condition of exposure is essential because the effects observed over the longer exposure might be considerably more pronounced over a shorter study duration.

Conclusion on the weight of evidence

70 As indicated above, the sources of information i. to vi. are relevant for the information requirement. However, the reliability of this infromation is hampered by the limited reporting of the information (studies ii. to vi.), issues with the use of information from analogue substances (studies iii. to vi.) and issues related to how the results were obtained in the studies (study i.) which increases the uncertainty of the conclusion for the Substance.

71 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.

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

73 Your comments to the draft decision regarding this information requirement are addressed under section 0.1.3 above.

2.3. Study design and test specifications

74 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.

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

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

3. Pre-natal developmental toxicity study in one species

77 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.).

3.1. Information provided

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

i. a reproduction/developmental toxicity screening test (2010, [redacted] according to the OECD TG 421 with the Substance.

79 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 ([redacted] 1983);

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

iv. studies in mice with intra-peritoneal exposure to the analogue substances phthalic anhydride and succinic anhydride during gestation days 8-10 ([redacted] 1982);

v. a study in rats with the analogue substance maleic anhydride during gestation days 6-15 ([redacted] 1986);

vi. a two-generation study in rats with the analogue substance maleic anhydride ([redacted] 1986).

80 You conclude from this information that "The available data for structural homologues of THPA indicate neither potential for teratogenic effects nor for reproduction toxicity in different species. These data, together with the available information of the OECD 421 study, are sufficient to permit evaluation of the respective endpoints and further tests would not be in line with current concerns regarding animal welfare and the use of animals in scientific experiments".

3.2. Assessment of the information provided

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

82 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.

83 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.

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

3.2.1. Aspect 1) to 3)

85 Pre-natal developmental toxicity (aspect 1) includes information after pre-natal 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).

86 Maternal toxicity (aspect 2) includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

87 Maintenance of pregnancy (aspect 3) includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

88 The source(s) of information i. to vi. provide relevant information on pre-natal developmental toxicity, but have the following deficiencies affecting the reliability of their contribution to the weight of evidence adaptation.

3.2.1.1. Reliability of the contribution of the studies ii. to vi.

89 The reliability of sources of information ii. to vi. is significantly affected by the deficiencies identified and explained under section 0.1.

90 Therefore, ECHA considers that the studies ii. to vi. cannot reliably contribute to your weight of evidence adaptation.

3.2.1.2. Reliability of the contribution of study i.

91 Investigations/specifications in a pre-natal developmental toxicity study (OECD TG 414) include:

a) each group should aim to have 20 female animals with implantation sites at

necropsy. Groups with fewer than 16 animals with implantation sites may be inappropriate.

b) examination of the foetuses for sex and body weight; external, skeletal, and soft tissue alterations (variations and malformations); number of resorptions and or live foetuses; and measurement of anogenital distance in live rodent foetuses.

92 In study i., the following investigations/specifications do not comply with the requirements of the OECD TG 414:

c) the study started with 10 animals per group;
d) the study has not investigated skeletal and soft tissue alterations (variations and malformations) nor measurement of anogenital distance in live rodent foetuses.

93 Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The lower statistical power of the study and unclarity on how the results were obtained introduce uncertainty in the results which must be considered.

Conclusion on the weight of evidence

94 As indicated above, the sources of information i. to vi. are relevant for the information requirement. However, the reliability of this infromation is hampered by the limited reporting of the information (studies ii. to vi.), issues with the use of information from analogue substances (studies ii. to vi.) and issues related to how the results were obtained in the studies (study i.) which increases the uncertainty of the conclusion for the Substance.

95 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.

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

97 Your comments to the draft decision regarding this information requirement are addressed under section 0.1.3 above.

3.3. Study design and test specifications

98 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.

4. Long-term toxicity testing on aquatic invertebrates

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

4.1. Information provided

100 You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification: "In accordance with REACH Regulation 1907/2006, Annex IX, Column 2, long-term tests on aquatic invertebrates need only be conducted if the outcome of the Chemical Safety Assessment indicates such a need. The substance will not be directly applied to water and, based on use patterns, exposure of aquatic systems is not expected to occur. The substance can be regarded as readily biodegradable, with rapid mineralisation to CO2 occurring in aerobic aquatic systems. Long-term toxicity studies are therefore not justified."

[5] ECHA Guidance R.7a, Section R.7.6.2.3.2.

4.2. Assessment of the information provided

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

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

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

103 Your adaptation is therefore rejected.

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

4.3. Study design and test specifications

105 The Substance is difficult to test since it is hydrolytically unstable (hydrolysis half-lives in purified water range from 7.62 to 2.57 minutes at 20°C within a pH range of 4-9). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Considering that the Substance is rapidly hydrolysable, it is important to take into account the relative toxicities of the parent test chemical and hydrolysis products to determine the appropriate test design and test media preparation methods for the Substance. Taking the rapid hydrolysis of the parent substance into account, it may be difficult to achieve and maintain the desired exposure concentrations of the Substance or its hydrolysis products.

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

5. Long-term toxicity testing on fish

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

5.1. Information provided

108 You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification: "In accordance with REACH Regulation 1907/2006, Annex IX, Column 2, long-term tests on fish need only be conducted if the outcome of the Chemical Safety Assessment indicates such a need. The substance will not be directly applied to water and, based on use patterns, exposure of aquatic systems is not expected to occur. The substance can be regarded as readily biodegradable, with rapid mineralisation to CO2 occurring in aerobic aquatic systems. Long-term toxicity studies with fish are therefore not justified and the expenditure of vertebrate test organisms is not ethically justified."

5.2. Assessment of the information provided

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

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

110 Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for

providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

111 In your comments on the draft decision, you state further that: "the outcome of the Chemical Safety Assessment does not indicate such a need based on the expected use patterns, the PEC/PNEC ratios resulting from EUSES modelling all returning an RCR less than 1." However, as explained above the Column 1 info requirement cannot be adapted based on the Column 2 referring to the Chemical Safety Assessment.

112 Your adaptation is therefore rejected.

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

5.3. Information provided in your comments on the draft decision

114 In your comments on the draft decision, you do not agree to perform the long-term toxicity to fish study as requested in the draft decision due to the following reasons:

115 you propose a tiered testing approach, to conduct first the long-term toxicity to aquatic invertebrates study (request 4) and then re-evaluate "the necessity for generation of data on long-term toxicity to fish [..] once the update of the dossier and CSR has been submitted to the Authority". You indicate your intention to update the Chemical Safety Assessment with the new PNECs calculated based on the results of the long-term toxicity to aquatic invertebrates study. You consider that no further long-term toxicity testing in fish will be needed "if PEC/PNEC is <1".

116 you refer to the "requirement to reduce testing on vertebrate species wherever possible". You recognise that minimisation of vertebrate testing is not on its own a legal ground for adaptation, but you remark that Annex XI, Section 1.2 states that "Where sufficient weight of evidence for the presence or absence of a particular dangerous property is available further testing on vertebrate animals for that property shall be omitted".

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

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

a. Regarding your proposal to omit the requested study if the updated Chemical Safety Assessment will not show the need for long-term fish toxicity testing:

119 These arguments do not refer to any of the adaptation possibilities in Annex XI. ECHA understands that your arguments refer to a possible adaptation under Annex IX, Section 9.1., Column 2. However, as explained above the Column 1 information requirement cannot be adapted based on the Column 2 referring to the Chemical Safety Assessment.

b. Regarding the arguments on reducing vertebrate testing and weight-of-evidence:

120 Adapting the information requirement in accordance with Annex XI, Section 1.2 requires that adequate and reliable documentation must be provided, including relevant justification and study records.

121 While in your comments you refer to weight of evidence for minimisation of vertebrate testing, in your dossier and in your comments you have provided no relevant justification nor documentation (e.g. study records) for this endpoint. Therefore, the conditions set out in Annex XI Section 1.2 are not met.

122 In conclusion, in your comments you have not provided any acceptable reason why long-term toxicity to fish should be omitted or conducted conditionally to long-term toxicity to

aquatic invertebrates (request 4). Since there is a data gap for both endpoints, ECHA requests that both studies are conducted.

5.4. Study design and test specifications

123 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.).

124 The OECD TG 210 specifies that, for difficult to test substances, the OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix 1.4.

Reasons related to the information under Annex X of REACH

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

125 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.).

6.1. Information provided

126 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 as described under section 3.1 above.

6.2. Assessment of the information provided

127 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.

128 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.

129 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.

130 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.

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

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

133 All the sources of information have been conducted in rodent species, i.e. mice, rats, guinea pigs.`

134 None of the sources of information provided have been generated in a non-rodent species. Information on PNDT properties in a second, non-rodent species is missing.

135 Therefore, it is not possible to conclude whether the Substance has or has not hazardous properties in relation to PNDT in two species.

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

137 Your comments to the draft decision regarding this information requirement are addressed under section 0.1.3 above.

6.3. Specification of the study design

138 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 3 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).

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.

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

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 Annexes VII to REACH, for registration at 1-10 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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

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