~~Confidential~~

Helsinki, 25 October 2022

Addressees
Registrant(s) of JS_85-42-7 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
27/03/2019

Registered substance subject to this decision ("the Substance")
Substance name: Cyclohexane-1,2-dicarboxylic anhydride
EC number: 201-604-9

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 1 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 IX of REACH

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

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

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

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

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

5. 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

General comments on the draft decision

1 In your comments on the draft decision you refer to the respiratory sensitisation properties of the Substance, and its status as Substance of very High Concern (SVHC) requiring stringent risk management measures to ensure workers protection. You specify that "exposure of professionals and consumers does not occur and professional and consumer uses are advised against". On that basis you consider that "further studies using mammalians to evaluate human health endpoints would not result in any change of the existing RMMs". ECHA understands that you refer to SVHC identification and existing RMMs to omit the following information requirements: Sub-chronic toxicity study (90-day), Pre-natal developmental toxicity study in one species, Pre-natal developmental toxicity study in a second species.

2 You also point at the recent ECHA's recommendation to include the Substance in Annex XIV of the REACH Regulation. You stress that once the Substance will be included in Annex XIV of the REACH and subject to Authorisation, the volume of the Substance produced or imported into the EU will drop significantly or may lead to the Substance being discontinued. These potential changes on the volumes brought on the EU market would affect the information requirements applicable to the Substance and not require testing according to REACH Annexes IX and X. ECHA understands that you refer to future changes in volumes to omit all information requirements addressed in this decision.

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

4 Consequences of SVHC identification and existing RMMs

5 In its decision on the case A-015-2019, the Board of Appeal considered that the fact that a substance is identified as a SVHC and that stringent risk management measures are in place to protect users from the sensitisation hazard do not affect the registrant's obligation to provide information on other endpoints, assess all the risks related to the substance, and develop appropriate risk management measures with regard to all those risks, and not only to respiratory sensitisation (Paragraph 45 of the ECHA Board of Appeal decision, case A-015-2019[2]). Therefore, your considerations that "further studies using mammalians to evaluate human health endpoints would not result in any change of the existing RMMs" do not constitute acceptable adaptations for the information requirements of Annex IX, 8.6.2, Annex IX 8.7.2 and Annex X, 8.7.2 addressed in this decision.

6 Changes in the volumes of the Substance produced/imported in the EU

7 You refer in your comments to hypothetical changes in the volumes of the Substance produced or imported in the EU as a result of the recommendation to include the Substance in Annex XIV of the REACH Regulation. The potential impact of changes in the tonnage band applicable for a substance produced or imported in Europe on the set of information requirements, and where applicable on the set of information requested in a compliance check decision, is determined by ECHA once such changes of volumes are declared by registrants.

8 One registrant informed ECHA that it had downgraded its registration dossier to a lower registration tonnage band and provided evidence to support this change. On the basis of the evidence provided ECHA concluded that the tonnage band downgrade is based on objective commercial considerations and can therefore be taken into account for the present decision-making procedure. The updated tonnage band of that registrant is therefore reflected in Appendix 3 of this decision.

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

Reasons related to the information under Annex IX of REACH

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

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

1.1. Information provided

10 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.

11 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 Substance (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;

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;

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.

12 You conclude from this information that "Considering all of these data together, a 90 day toxicity study with HHPA 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.

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

1.2. Assessment of the information provided

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

15 Annex XI, Section 1.2 states that there may be sufficient weight of evidence 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.

16 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.

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

18 You have provided a justification for the weight of evidence adaptation as follows:

19 "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 HHPA".

20 However, your justification does 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 property investigated by the required study.

21 Your adaptation is rejected because of lack of adequate and reliable (concise) documentation for the justification of the weight of evidence adaptation and the information requirement is not fulfilled.

22 Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

23 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.

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

1.2.1. Aspect 1) in-life observations

25 In-life observations 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).

26 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.

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

27 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.

28 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:

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

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

31 In your justification of your adaptation you provide a short description of information on the Substance and on analogue substances (studies ii. to vi.) that you include in your weight of evidence approach. These high level summaries confirm that these studies provide information which is relevant to the information requirement of Annex IX, Section 8.6.2. for a sub-chronic (90-day) toxicity study.

32 However, you have not provided robust study summaries for each of these studies. The description of the studies ii., iv., v. and vi. in the WHO CICAD report 75 included in your technical dossier do not provide more information than what is included in your justification.

33 Furthermore, you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the studies ii. to vi in the form of robust study summaries in your dossier.

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

35 In the absence of such information, ECHA considers that the studies ii. to vi. cannot reliably contribute to your weight of evidence adaptation.

1.2.1.2. Reliability of the contribution of the information on analogue substances – studies iii. to vi

36 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 approach, it would have to meet the requirements for Grouping of substances and read-across approach.

37 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).

38 Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[3] and related documents[4, 5].

39 Prediction of toxicological properties

40 You provide a justification for using information on analogue substances in separate endpoint study records under section 7.5.1 in IUCLID and in the corresponding section of your Chemical Safety Report.

41 You read-across to the Substance from the following source substances:

- tetrahydromethylphthalic anhydride (MTHPA);

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

- trimellitic anhydride (TMA).

42 You provide the following reasoning for the prediction of toxicological properties in the endpoint study records provided for this adaptation: "HHPA 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."

43 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.

44 ECHA notes the following shortcomings with regards to prediction of toxicological properties.

1.2.1.3. Missing supporting information

45 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).

46 Supporting information must include bridging studies to compare properties of the substances.

47 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 the Substance and source 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).

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

49 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 iii. to vi. included in the endpoint study record provided for this adaptation do not allow for an independent assessment of the reliability of these studies.

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

51 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 adaptation.

1.2.1.4. Reliability of the contribution of study i.

52 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.

53 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.

54 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 studies 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.

1.2.2. Aspect 2) blood chemistry

55 Information on blood chemistry 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).

56 The sources of information i. to vi. provide relevant information on aspect 2).

57 However, these sources of information have deficiencies affecting their reliability. Specifically, the reliability issues identified for aspect 1) and addressed in sections 1.2.1.1 to 1.2.1.4 above apply equally to this aspect.

1.2.3. Aspect 3) organ and tissue toxicity

58 Organ and tissue toxicity 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).

59 The sources of information i. to vi. provide relevant information on aspect 3).

60 However, these sources of information have deficiencies affecting their reliability. Specifically, the reliability issues identified for aspect 1) and addressed in sections 1.2.1.1 to 1.2.1.4 above apply equally to this aspect.

1.3. Conclusion on the weight of evidence

61 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.

62 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.

1.4. Information provided in your comments on the draft decision

63 For the reasons explained in Section 0 above, in your general comments you have not provided acceptable arguments to omit the requested study.

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

1.5. Study design and test specifications

65 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.

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

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

2. Pre-natal developmental toxicity study in one species

68 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.).

2.1. Information provided

69 You have provided a reproduction/developmental toxicity screening test (2010, [redacted] conducted with the Substance according to the OECD TG 421 .

2.2. Assessment of the information provides

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

2.2.1. Study not adequate for the information requirement

71 (Eco)toxicological studies must comply with a recognised test method (Art. 13(3) of REACH), in this case the OECD TG 414. Such study must cover the key parameters of the corresponding OECD test guideline (Art. 13(3) of REACH). Therefore, the following specifications must be met:

a. 20 female animals with implantation sites for each test and control group;

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/ measurement of anogenital distance in live rodent foetuses.

72 The study that you have submitted is described as "reproduction/ developmental toxicity screening test". This study has been conducted using OECD TG 421 which is a screening test rather than a conclusive developmental toxicity study. In any case, that study does not cover the key parameters of the OECD TG 414 such as:

a. a statistical power equivalent to the OECD TG 414: the study provided has 10 animals in each group;

b. skeletal and soft tissue alterations (variations and malformations).

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

2.3. Information provided in your comments on the draft decision

74 For the reasons explained in Section 0 above, in your general comments you have not provided acceptable arguments to omit the requested study.

2.4. Study design and test specifications

75 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species. The study must be performed with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

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

3. Long-term toxicity testing on aquatic invertebrates

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

3.1. Information provided

78 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 is readily biodegradable, with rapid mineralisation to CO2 occurring in aerobic aquatic systems. Long-term toxicity studies are therefore not justified."

3.2. Assessment of the information provided

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

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

80 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).

81 Your adaptation is therefore rejected.

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

3.3. Information provided in your comments on the draft decision

83 For the reasons explained in Section 0 above, in your general comments you have not provided acceptable arguments to omit the requested study. ECHA acknowledges that you agree to conduct the requested study "if ECHA declines the comments given under "general comment on the draft decision"".

3.4. Study design and test specifications

84 The Substance is difficult to test since it is hydrolytically unstable (hydrolysis half-life in purified water < 5 minutes at 25°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.

85 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.

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

4. Long-term toxicity testing on fish

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

4.1. Information provided

88 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 is 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."

4.2. Assessment of the information provided

89 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

90 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).

91 Your adaptation is therefore rejected.

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

4.3. Information provided in your comments on the draft decision

93 For the reasons explained in Section 0 above, in your general comments you have not provided acceptable arguments to omit the requested study.

94 Furthermore, in your comments on the draft decision, you propose to conduct the long-term toxicity to aquatic invertebrates study (request 3) "before a long-term fish toxicity test is considered". You do not agree to perform the long-term toxicity to fish study as requested in the draft decision due to the following reasons:

a. "*to reduce vertebrate testing in an integrated testing strategy and especially because the available data on the Substance and on other cyclic anhydrides do not indicate*

that fish are more acutely sensitive than invertebrates";

b. you propose "to re-evaluate the necessity for the generation of data on long-term toxicity on 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".

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

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

a. Regarding the arguments on minimisation of vertebrate testing and fish being less sensitive than invertebrates:

97 Your justification to omit the study does not refer to any of the adaptation possibilities in Annex XI. Therefore, the arguments provided in your comments are not appropriate to adapt the information requirement.

b. 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:

98 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.

99 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 3). Since there is a data gap for both endpoints, ECHA requests that both studies are conducted.

4.4. Study design and test specifications

100 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.).

101 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' under Appendix 1.3.

Reasons related to the information under Annex X of REACH

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

102 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.).

5.1. Information provided

103 You have adapted this information requirement by using Column 2 of Annex IX, Section 8.7. whereby "The study shall be initially per formed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data."

104 To support the adaptation, you have provided your considerations on the need to perform a study in a second species. Your considerations are based on:

- The identification of a NOAEL of 1000 mg/kg/d in a reproduction/developmental toxicity screening test (2010, [redacted] conducted with the Substance according to the OECD TG 421;
- The classification of the Substance as skin and respiratory sensitiser. You consider that "sensitisation is to be regarded as the most sensitive end-point for which no DNEL can be derived due to the lack of dose-response data" and that a qualitative approach must be applied to assess and control the risks;
- A review of the utility of testing in a second species for pharmaceutical compounds has been undertaken in a project led by the International Life Sciences Institute-Health and Environmental Sciences Institute (ILSI-HESI) Development and Reproductive Toxicology (DART) Technical Committee. This review concluded that "in the majority of cases the 2nd species does not add significantly to the overall judgement on developmental hazard' (Theunissen et al., 2014)".

105 You conclude from this information that "information is available from the rat to conclude that no hazard for toxicity to development/teratogenicity has been identified. Furthermore, the outcome of a comparative analysis of data on pharmaceutical compounds suggest that the 2nd species does not add significant information for the assessment of developmental effects.

106 Therefore, referring to Regulation (EC) No. 1907/2006, Annex IX, 8.7.2 Column 2, performing a prenatal developmental toxicity study in a 2nd species is considered not to add new information for hazard assessment and therefore is scientifically and, considering concerns regarding the use of vertebrate animals for experimental purposes, morally unjustified."

5.2. Assessment of the information provided

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

108 In order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species.

109 A pre-natal developmental toxicity study in a second species is a standard information requirement at Annex X unless one or more of the adaptations in Section 8.7 of Annex X or Annex XI apply, taking into account the results of the test in the first species or any other relevant avalable information.

110 Your adaptation refers to the provisions of Annex IX, Column 2, Section 8.7.2. Since your Substance is registered at more than 1000 tpa, the information requirement of Annex X,

8.7.2 for a PNDT study in a second species applies. This standard information requirement cannot be adapted according to Annex IX, Column 2, Section 8.7.2.

5.3. Specification of the study design

111 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 2 in this decision).

5.4. Information provided in your comments on the draft decision

112 In your comments on the draft decision you refer to the provisions of Annex IX, 8.7.2, column 2 whereby a decision on the need to perform a study in a second species at the 100-1000 tpa or at the next tonnage level needs to be made. You indicate that "if ECHA declines the comments given under "general comment on the draft decision" the registrants propose a sequential testing strategy". You do not agree to perform the requested pre-natal developmental toxicity study in a second species as requested in the draft decision. You propose to await the outcome of the pre-natal developmental toxicity study in a first species to determine whether or not these results trigger a classification for developmental toxicity, in which case a further study in a second species would not be required. In case no classification is warranted on the basis of the information from the PNDT study in a first species, you indicate that you would submit a testing proposal for a PNDT study in a second species.

113 You specify that in case ECHA would not agree to your proposed sequential testing strategy, the timeline to submit the information requested in this decision should be extended to 36 months to allow for sequential testing in two species.

114 For the reasons explained in Section 0 above, in your general comments you have not provided acceptable arguments to omit the requested study.

115 Furthermore, a pre-natal developmental toxicity study in a first species is a standard information requirement under Annex IX of REACH and pre-natal developmental toxicity (PNDT) studies in a second species is an information requirement under Annex X. This means that the provisions of Annex IX, 8.7.2, column 2 on the need to consider whether a PNDT study in a second species is needed do not apply. However, in line with your comment, according to Annex X, 8.7, column 2, the PNDT study in a second species would not need to be conducted in case the results from the PNDT study in a first species would meet the criteria for classification of the Substance as toxic to reproduction category 1A or 1B: may damage the unbord child. Therefore your proposal to conduct the study sequentially is scientifically sound. Since the studies in both species are requested in this compliance check decision, no testing proposal is to be submitted for the PNDT study in a second species.

116 You request an extension of the timeline to provide the information to 36 months in order to conduct both PNDT sequentially. ECHA considers that the timeline set in the decision allows for sequential testing. In the absence of documentary evidence to justify your request, such as statements from testing laboratories including scheduling timelines for the studies, your request is rejected and the deadline is not modified.

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) and the deadline.

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]

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