~~Confidential~~

Helsinki, 08 December 2023

Addressee(s)
Registrant(s) of JS_EC915-680-2 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
18 May 2022

Registered substance subject to this decision ("the Substance")
Substance name: Reaction mass of phosphonic acid, methyl-, bis[(5-ethyl-2-methyl-2,2-dioxido-1,3,2-dioxaphosphorinan-5-yl)methyl] ester with (5-ethyl-2-methyl-2-oxido-1,3,2-dioxaphosphorinan-5-yl)methyl methyl methylphosphonate
EC/List number: 915-680-2

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***15 March 2027***.

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

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

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

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

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

4. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: EU C.4. A/B/C/D/E/F/OECD TG 301A/B/C/D/E/F or EU C.29./OECD TG 310).

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

5. In vitro micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei;

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

7. Justification for an adaptation of the short-term repeated dose toxicity study (28 days) (Annex VIII, Section 8.6.1., Column 2) based on the request 10 below.

   If the sub-chronic toxicity study (90 days) is not requested:

   Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.) by oral route, in rats, to be combined with the screening for reproductive/developmental toxicity requested below.

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

9. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203).

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

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

11. 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);

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

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

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 registrant with the Registration number 01-2120770258-48-0002 is not requested to provide the information under Request 2 (Short-term toxicity on aquatic invertebrates), because it has opted out from the joint submission for that information requirement.

The addressee(s) 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 request(s)
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 request(s)

Contents

Reasons common to several requests

0.1. Assessment of (Q)SAR information

1 You have adapted the following information requirements by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs):

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2)
- Short-term toxicity to fish (Annex VIII, Section 9.1.3.)
- Long-term toxicity to aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity to fish (Annex IX, Section 9.1.6.)

2 To support the adaptation, you have provided predictions with ECOSAR 1.11 including QMRF document (two QMRFs for each short-term toxicity prediction and growth inhibition to aquatic plants prediction, one QMRF for each long-term prediction) and two QPRF documents for two constituents of the Substance for each of the information requirements above.

3 ECHA has considered the scientific and regulatory validity of your (Q)SAR adaptation(s) in general before assessing the specific standard information requirements in the following appendices.

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

(1) the prediction needs to be derived from a scientifically valid model,
(2) the substance must fall within the applicability domain of the model,
(3) results need to be adequate for the purpose of risk assessment or classification and labelling, and
(4) adequate and reliable documentation of the method must be provided.

5 Regarding these conditions, we have identified the following issue(s):

0.1.1. (Q)SAR adaptation rejected

0.1.1.1. Inadequate documentation of the model (QMRF and QPRF)

6 Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain;

7 In addition, the Guidance (R.6.1.10.1) states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the identification of the specific sub model or algorithm applicable to the specific chemical
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

8 The provided QMRF and QPRF documents do not inform on the definition of the algorithm (i.e. in the case of ECOSAR, the class specific model) from which the prediction is generated.

9 In addition, you did not provide information on the identities of close analogues in the provided QPRFs.

10 In absence of such information, ECHA cannot assess the reliability of the predictions and validity of the models and establish that the provided QSARs can be used to meet the information requirements.

0.1.2. Conclusion on the (Q)SAR adaptation

11 Based on the above, your (Q)SAR adaptation under Annex XI, Section 1.3. is rejected.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

12 An in vitro gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

1.1. Information provided

13 You have provided an in vitro gene mutation study in bacteria (1976) with the Substance.

1.2. Assessment of the information provided

1.2.1. Assessment of Annex XI, Section 1.1.2. adaptation

14 Under Annex XI, Section 1.1.2., data from experiments generated prior to the 1st of June 2008 and not carried out according to GLP or the test guideline normally required for the information requirement must be considered equivalent to data generated from the test method if the following condition(s) are met:

(1) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

15 For this information requirement, the data from the experiment must have adequate and reliable coverage of the key parameters of the OECD TG 471. Therefore, the following specifications must be met:

a) the test is performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101);
b) concurrent strain-specific positive controls, both with and without metabolic activation, are included in each assay and the number of revertant colonies per plate induced by the positive controls demonstrates the effective performance of the assay.

16 In the study provided,

a) the test was performed with the strains *S. cerevisiae* (strain D4), Salmonella typhimurium strains TA 1535, TA1537, TA1538, TA-98 and TA-100. (i.e., the strain(s) *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) are missing);
b) no information is provided on the identity of the concurrent strain-specific positive controls included in the study. While you report the observation of positive response with the positive controls used in the study, the adequacy of the positive control for the test models used cannot be ascertained without information on their identity and in turn the effective performance of the assay cannot be established.

17 Therefore, the data provided do not have adequate and reliable coverage of the key parameters of the OECD TG 471.

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

1.3. Specification of the study design

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

2. Short-term toxicity testing on aquatic invertebrates

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

2.1. Information provided

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

(i) a prediction from QSAR (ECOSAR 1.11), 27/09/2019.

2.2. Assessment of the information provided

2.2.1. (Q)SAR adaptation rejected

22 As explained in Section 0.1., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

23 Therefore, this information requirement is not fulfilled.

2.1. Information regarding data sharing

24 Another registrant's registration for the Substance contains a short-term toxicity testing on aquatic invertebrates (1998) which is adequate for this information requirement. You may consider sharing this information.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

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

(i) a prediction from QSAR (ECOSAR 1.11), 27/09/2019.

3.2. Assessment of the information provided

3.2.1. (Q)SAR adaptation rejected

27 As explained in Section 0.1., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

28 Therefore, this information requirement is not fulfilled.

4. Ready biodegradability

29 Ready biodegradability is an information requirement in Annex VII to REACH (Section 9.2.1.1.).

4.1. Information provided

30 You have provided:

(i) a ready biodegradability study (OECD TG 301 B, 1998) with the Substance.

4.2. Assessment of the information provided

4.2.1. The provided study does not meet the specifications of the test guideline

31 To fulfil the information requirement, a study must comply with the OECD TG 301 or 310 (Article 13(3) of REACH). Therefore, for a study according to OECD TG 301 B, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) determination is carried out at least in duplicate;

Reporting of the methodology and results

b) the concentration of the inoculum in the test is reported;

c) the source of the inoculum, its concentration in the test and any pre-conditioning treatment are reported;

d) the test temperature and pH is reported;

e) the results of measurements at each sampling point in each replicate is reported in a tabular form;

f) the calculation of the $ThCO_2$ is described and justified;

g) the inorganic carbon content (IC) and total carbon content (TC) of the test material suspension in the mineral medium at the beginning of the test is reported;

Validity criteria

h) the following validity criteria must be met:

- the degradation of the reference compound has reached the pass level by day 14;
- the difference of extremes of replicate values of the removal of the test material at the plateau, at the end of the test or, if appropriate, at the end of the 10-d window is ≤ 20%;
- in the toxicity control, the degradation of the reference substance has reached ≥ 35% (based on DOC) or ≥ 25% (based on ThOD or $ThCO_2$) by day 14;
- the test material is the sole source of added organic carbon;

- OECD 301B^^
- the inorganic carbon content (IC) of the test material suspension in the mineral medium at the beginning of the test is < 5% of the total carbon (TC);
- the total CO_2 evolution in the inoculum blank at the end of the test does not normally exceed 40 mg CO_2/L;

32 You did not provide the information listed above (a-h) for study i.

33 Based on the above the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically you have not provided tabulated data or details on the inoculum, test conditions, replicates, and controls. Furthermore, you did not disclose information on the validity criteria of the study. On this basis, it is not possible to perform independent assessment of the study validity.

34 On this basis, the specifications of OECD TG 301 B are not met.

35 Therefore, the information requirement is not fulfilled.

4.3. Study design

36 To fulfil the information requirement, the test method(s) according to OECD TG 301B/C/D/E/F or OECD TG 310 are in general appropriate. You can choose any of these methods, but you must ensure that the Substance is within the applicability domain of the test method chosen.

37 The revised introduction to the OECD Guidelines For Testing Of Chemicals, Section 3 Part I states that ready biodegradability tests are intended for pure substances but may also be relevant, on a case-by-case basis, to mixtures of structurally similar chemicals (i.e. which are composed of constituents expected to show similar degradation kinetics).

38 However, such tests are not generally applicable for complex mixtures or substances (i.e. UVCB or multi-constituent substances) containing different types of constituents.

39 For the generation of information on ready biodegradability, you must consider the level of information required for the purposes of classification and labelling and, if applicable to your registration, the PBT/vPvB assessment and the exposure assessment/risk characterisation.

40 In order to conclude on which of constituents of the Substance are and which are and which are not readily biodegradable, you may have to consider conducting more than one study using selected individual constituents and/or fractions. If you choose to test one (or more) fraction(s) of the Substance, you must provide a justification that their constituents within chosen fraction(s) are similar enough so that similar degradation kinetics can be assumed.

41 If you decide to conduct a single study in order to prove that all constituents of the Substance are readily biodegradable, you must provide a justification that the selected constituent/fraction can be considered a reasonable worst-case for the Substance as a whole in terms of degradation kinetics.

42 Justification for selection of relevant constituent and/or fractions for the testing, must consider degradation kinetics of constituents of the Substance based, as minimum, on the similarity/differences of the chemical structures and the physico-chemical properties of constituents of the Substance. For that purpose, tools and approaches mentioned in Guidance on IRs and CSA, Sections R.7b and R.11 should be considered.

Reasons related to the information under Annex VIII of REACH

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

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

5.1. Information provided

44 You have provided an in vitro cytogenicity study (2021) with the Substance.

5.2. Assessment of the information provided

45 To fulfil the information requirement, the study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test conducted in mammalian cells. The study must comply with the OECD TG 473 or the OECD TG 487, respectively (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) at least 3 concentrations are evaluated, in absence and in presence of metabolic activation;
b) at least 2000 cells are scored per concentration;
c) data on the cytotoxicity and the frequency of micronuclei for the treated and control cultures is reported;
d) to conclude on a negative outcome, a negative response is obtained in all three experimental conditions described in paragraph 38 of the OECD TG 487, using a short-term treatment with and without metabolic activation and long-term treatment without metabolic activation.

46 In the robust study summary provided for the study included in your dossier:

a) No information is provided on the number of concentrations which were evaluated in absence and in presence of metabolic activation;
b) No information is provided on the number cells which were scored per concentration;
c) data on the cytotoxicity and/or the frequency of micronuclei for the treated and control cultures were not reported;
d) No information is provided on the experimental conditions as described in paragraph 38 of the OECD TG 487 to conclude on a negative outcome.

47 The information provided does not cover the specifications(s) required by the OECD TG 487. Therefore, the information requirement is not fulfilled.

5.3. Specification of the study design

48 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the in vitro mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the in vitro mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations in vitro. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2).

49 Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential in vitro.

50 Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

5.3.1. Assessment of aneugenicity potential

51 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

52 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) 'At the present time, no aneugens are known that require metabolic activation for their genotoxic activity' (paragraph 34).

6. In vitro gene mutation study in mammalian cells

6.1. Triggering of the information requirement

53 Your dossier contains data for an in vitro gene mutation study in bacteria, and data for an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study.

54 The information for the in vitro gene mutation study in bacteria and for the in vitro cytogenicity study in mammalian cells or in vitro micronucleus study provided in the dossier are rejected for the reasons provided in requests 1 and 5.

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

56 Consequently, you are required to provide information for this information requirement, if the in vitro gene mutation study in bacteria and the in vitro micronucleus study provide a negative result.

6.2. Information provided

57 You have provided:

(i) an *in vitro* gene mutation study in bacteria (1976) with the Substance;

(ii) an in vivo germ cell gene mutation study (1979) with the Substance.

6.3. Assessment of the information provided

6.3.1. Assessment of Annex XI, Section 1.1.2. adaptation (study i)

58 Under Annex XI, Section 1.1.2., data from experiments generated prior to the 1st of June 2008 and not carried out according to GLP or the test guideline normally required for the information requirement must be considered equivalent to data generated from the test method if the following condition(s) are met:

(1) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

59 For this information requirement, the data from the experiment must have adequate and reliable coverage of the key parameters of the OECD TG 476 (Guidance on IRs and CSA, Table.7.7-2) (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) at least 4 concentrations are evaluated, in absence and in presence of metabolic activation;
b) a positive control is included in the study;
c) data on the cytotoxicity and the mutation frequency for the treated and control cultures are reported.

60 In study (i):

a) The number of concentration evaluated in absence and in presence of metabolic activation is not specified;
b) no positive control was included in the study;
c) data on the cytotoxicity and the mutation frequency for the treated and control cultures were not reported.

61 Therefore, the data provided do not have adequate and reliable coverage of the key parameters of the OECD TG 476.

62 Based on the above, the adaptation is rejected.

6.3.2. The provided adaptation does not meet the criteria of Annex VIII, Section 8.4.3., Column 2 (study ii).

63 Under Annex VIII, Section 8.4.3., Column 2, the study may be omitted if adequate data from a reliable in vivo mammalian gene mutation test are available. The Guidance on IRs and CSA, Section R.7.7.6.3. clarifies that the in vivo study must be a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay (TGR), performed according to the OECD TG 488. This test investigates gene mutations using reporter genes.

64 The study (ii) is an in vivo insect germ cell study performed according to the OECD TG 477.

65 The study (ii) is not a mammalian gene mutation test, i.e. not a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay.

66 Therefore, the requirements of Annex VIII, Section 8.4.3., Column 2 are not met and your adaptation is rejected.

67 For the reasons presented above, the information requirement is not fulfilled

6.4. Specification of the study design

68 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.

7. Short-term repeated dose toxicity (28-day)

69 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1. This information may take the form of a study record or a valid

adaptation in accordance with either a specific adaptation rule under Column 2 or a general adaptation rule under Annex XI.

7.1. Information provided

70 You have adapted this information requirement by using Column 2 of Annex VIII, Section 8.6.1. To support the adaptation, you have provided a sub-chronic (90-day) toxicity study (1979) with the Substance.

7.2. Assessment of the information provided

71 Under Annex VIII, Section 8.6.1., Column 2, Paragraph 1, Indent 1, the study may be omitted if a reliable sub-chronic (90 days) or chronic toxicity study is available or proposed by the registrant.

72 Under Annex XI, Section 1.1.2., data from experiments generated prior to the 1st of June 2008 and not carried out according to GLP or the test guideline normally required for the information requirement must be considered equivalent to data generated from the test method if the following condition(s) are met:

(1) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

73 For this information requirement, the data from the experiment must have adequate and reliable coverage of the key parameters of the OECD TG 408. Therefore, the following specifications must be met:

a) clinical signs are observed daily and functional observations (i.e. sensory activity, grip strength and motor activity assessments) are made during week 11 or later;
b) haematological and clinical biochemistry tests are performed as specified in the OECD TG 408;
c) the oestrus cycle in females is examined at necropsy;
d) terminal organ and body weights are measured;
e) gross pathological examinations as specified in the OECD TG 408 are performed;
f) full histopathology is performed as specified in the OECD TG 408.

74 In study (i):

a) No information on the nature of the clinical signs and functional aspects examined were reported.
b) No information on the nature of the haematology and clinical biochemistry investigations performed were reported.
c) No information on whether oestrus cyclicity was assessed was reported;
d) No information on the terminal organ weights and organ/body weight ratios which were recorded was reported;
e) No information on the gross pathology aspects which were covered was reported;
f) No information on the histopathology items which were studied was reported.

75 The data provided do not have adequate and reliable coverage of the key parameters of the OECD TG 408. Therefore the study provided is not considered to be a reliable sub-chronic (90 days) study.

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

7.3. Study design

77 The OECD TG 407 is an appropriate guideline for fulfilling this information requirement.

78 Following the criteria provided in Annex VIII, Section 8.6.1., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.1., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance.

79 According to the OECD TG 407, the rat is the preferred species.

80 The information requirement for the screening study for reproductive/developmental toxicity is not fulfilled for the reasons explained under request 4.

81 When there is no information available neither for the 28-day repeated dose toxicity (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) would allow to fulfil both information requirements, and is preferred to ensure that unnecessary animal testing is avoided. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

7.3.1. Justification for an adaptation of the short-term repeated dose toxicity study (Annex VIII, Section 8.6.1., Column 2)

82 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 10).

83 According to Annex VIII, Section 8.6.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not need to be conducted.

84 Therefore, to comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to provide a justification for adaptation, as provided in Annex VIII, Section 8.6.1., Column 2.

85 In case the adopted decision no longer contains a request for a 90-day study, you are required to provide a 28-day study.

Therefore, you are requested to either submit:

- a justification for the adaptation according to Annex VIII, Section 8.6.1., Column 2, based on request 10; or
- a 28-day study to be combined with the screening for reproductive/developmental toxicity in case the 90-day study is not requested in the adopted decision.

8. Screening for reproductive/developmental toxicity

86 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1.

8.1. Information provided

87 You have provided a screening for reproductive / developmental toxicity study (1979) with the Substance (study i).

88 Furthermore, you have adapted this information requirement by using Column 2 of Annex VIII, Section 8.7.1. To support the adaptation, you have provided the following information:

(ii) A waiving statement indicating that "t*he study does not need to be conducted because a pre-natal developmental toxicity study is available*";
(iii) A pre-natal developmental toxicity study (1978) with the Substance.

8.2. Assessment of the information provided

8.2.1. Assessment of Annex XI, Section 1.1.2. adaptation (study i)

89 Under Annex XI, Section 1.1.2., data from experiments generated prior to the 1st of June 2008 and not carried out according to GLP or the test guideline normally required for the information requirement must be considered equivalent to data generated from the test method if the following condition(s) are met:

(1) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);

(1) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3).

90 For this information requirement, the data from the experiment must have adequate and reliable coverage of the key parameters of the OECD TG 421 (Guidance on IRs and CSA, Table.7.7-2) (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) at least 10 male and 12-13 female animals are included for each dose and control group;
b) the exposure duration is at least four weeks for males, including a minimum of two weeks prior to mating, and approximately 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation;
c) body weights are measured at least weekly;
d) food consumption is measured at least weekly;
e) the nature, severity, and duration of clinical signs observed daily are reported;
f) gross pathology of reproductive organs is performed, and the presence or absence, incidence and severity of abnormalities is evaluated;
g) histopathology of reproductive organs and tissues is performed, and the presence or absence, incidence and severity of abnormalities is evaluated.
h) parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition and lactation are reported;
i) oestrous cycles are monitored;
j) offspring parameters such as number and sex of pups, stillbirths and live births, gross abnormalities, pup body weight, litter weight, anogenital distance, nipple retention in male pups are reported.

91 In study (i):

a) Only females were dosed in this study. No males were included in any of the test and control groups ;
b) No information on the duration of treatment, including pre-mating exposure is reported;
c) data on body weights, body weight changes are missing;
d) data on food consumption are missing;
e) data on clinical signs, including their nature, severity, and duration, are not reported;
f) data on gross pathology findings, including incidence and severity of abnormalities, are not reported:
g) data on histopathology findings, including incidence and severity of abnormalities, are not reported.
h) data on parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition and lactation are missing;
i) data on oestrous cycles is missing;
j) data on number and sex of pups, stillbirths and live births, gross abnormalities, pup body weight, litter weight, anogenital distance, nipple retention in male pups is missing.

92 Therefore, the data provided do not have adequate and reliable coverage of the key parameters of the OECD TG 421 and do not cover an exposure duration comparable to or longer than the one specificied in the OECD TG 421.

93 Based on the above, the adaptation is rejected.

8.2.2. The provided adaptation does not meet the criteria of Annex VIII, Section 8.7.1., Column 2 (study ii).

94 Under Annex VIII, Section 8.7., Column 2, the study does not need to be conducted if a pre-natal developmental toxicity study (OECD TG 414) referred to in Annex IX, Section 8.7.2. is available.

95 The study (iii) is a pre-natal developmental toxicity study.

96 However, for the reasons explained in request 11 the study (iii) is not reliable.

97 Based on the above, the adaptation is rejected.

8.3. Study design

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

99 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex VIII, Section 8.7.1., Column 1).

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

101 When there is no information available neither for the 28-day repeated dose toxicity (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) would allow to fulfil both information requirements, and is preferred to ensure that unnecessary animal testing is avoided. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

102 In case the adopted decision no longer contains a request for a sub-chronic (90 days) study (e.g. as a result of an overall tonnage band change of the joint submission) and the 28-day study must be performed, a screening study for reproductive/developmental toxicity performed according to the OECD TG 422 is required, as it will fulfil both information requirements.

9. Short-term toxicity testing on fish

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

9.1. Information provided

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

(i) a prediction from QSAR (ECOSAR 1.11), 27/09/2019.

9.2. Assessment of the information provided

9.2.1. (Q)SAR adaptation rejected

105 As explained in Section 0.1., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

106 Therefore, this information requirement is not fulfilled.

Reasons related to the information under Annex IX of REACH

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

107 A sub-chronic toxicity study (90 days) is an information requirement under Annex IX, Section 8.6.2.

10.1. Information provided

108 You have provided a sub-chronic (90 days) toxicity study (1979) with the Substance.

10.2. Assessment of the information provided

109 Under Annex XI, Section 1.1.2., data from experiments generated prior to the 1st of June 2008 and not carried out according to GLP or the test guideline normally required for the information requirement must be considered equivalent to data generated from the test method if the following condition(s) are met:

(1) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

110 For this information requirement, the data from the experiment must have adequate and reliable coverage of the key parameters of the OECD TG 408.

111 The provided study is described as a sub-chronic (90 days) study.

112 However, for the reasons explained in request 7 the study is not a reliable sub-chronic (90 days) study.

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

10.3. Study design

114 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance.

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

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

11. Pre-natal developmental toxicity study in one species

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

11.1. Information provided

118 You have provided a pre-natal developmental toxicity study in rats (1978) with the Substance.

11.2. Assessment of the information provided

119 Under Annex XI, Section 1.1.2., data from experiments generated prior to the 1st of June 2008 and not carried out according to GLP or the test guideline normally required for the information requirement must be considered equivalent to data generated from the test method if the following condition(s) are met:

(1) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3); and/or

120 For this information requirement, the data from the experiment must have adequate and reliable coverage of the key parameters of the OECD TG 414. Therefore, the following specifications must be met:

a) the nature, severity, and duration of the clinical signs are observed daily;
b) the dams are examined for any structural abnormalities, gravid uterus weight, and uterine content.

121 In the study provided,

a) data on clinical signs, including nature and severity, are missing;
b) data on the examination of the dams, including incidence and severity, are missing;

122 Therefore, the data provided do not have adequate and reliable coverage of the key parameters of the OECD TG 414.

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

11.3. Study design

124 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species.

125 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1).

12. Long-term toxicity testing on aquatic invertebrates

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

12.1. Information provided

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

(i) a prediction from QSAR (ECOSAR 1.11), 27/09/2019

12.2. Assessment of the information provided

12.2.1. (Q)SAR adaptation rejected

128 As explained in Section 0.1., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

129 Therefore, this information requirement is not fulfilled.

13. Long-term toxicity testing on fish

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

13.1. Information provided

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

(i) a prediction from QSAR (ECOSAR 1.11), 27/09/2019

13.2. Assessment of the information provided

13.2.1. (Q)SAR adaptation rejected

132 As explained in Section 0.1., your adaptation based on Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) under Annex XI, Section 1.3. is rejected.

133 Therefore, this information requirement is not fulfilled.

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).
Guidance for monomers and polymers; ECHA (2023).
***Guidance on intermediates*;** ECHA (2010).
All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 02 May 2022.

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

ECHA notified you of the draft decision and invited you to provide comments.

ECHA did not receive any comments within the commenting period.

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

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

Appendix 3: Addressee(s) of this decision and their corresponding information requirements

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

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

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

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[2].

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

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

[2] https://echa.europa.eu/practical-guides

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[3].

2. General recommendations for conducting and reporting new tests

2.1. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in Guidance on IRs & CSA, Section R.11.4.2.2, you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesize its relevant constituents and/or fractions.

References to Guidance on REACH and other supporting documents can be found in Appendix 1.

[3] https://echa.europa.eu/manuals