~~Confidential~~

Helsinki, 25 November 2022

Addressees
Registrant(s) of JS 68958-77-0 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
10 February 2022

Registered substance subject to this decision ("the Substance")
Substance name: 4,4'-Isopropylidenediphenol, polymer with 1-chloro-2,3-epoxypropane, propane-1,2-diol acrylate and succinic anhydride
EC number: 500-240-0

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 A rticle 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***2 March 2026***.

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

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

1. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2)

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

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

3. If negative results are obtained in test performed for the information requirement of 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);

4. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested below (Annex VIII, Section 8.6.1.);

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

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

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

7. 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);

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

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

Information required depends on your tonnage band

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

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

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

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

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

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. *Assessment of the read-across approach*

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

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.);
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.);
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).

2 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following sections.

3 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.

4 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1. *Predictions for toxicological properties*

5 You provide a read-across justification document in IUCLID Section 13.

6 You predict the properties of the Substance from information obtained from the following source substance(s): 4,4'-isopropylidenediphenol, oligomeric reaction products with 1-chloro-2,3-epoxypropane, esters with acrylic acid' (DGEBADA; EC 500-130-2).

7 You provide the following reasoning for the prediction of toxicological properties: you state that the Substance and the source substance "share common properties". You reason that "*the main constituent of the target and the source substance share a common core, [redacted]*" and "*key functional groups, such as acrylate, aryl, alkane, alcohol, carboxylic acid ester and ether groups*". Further, you state that the Substance and the source substance have common structural alerts and reactivity and that "*the constituents of the target and the source substances are predicted to be metabolised via similar pathways*". You concluded that "*Based on the physico-chemical properties as well as molecular weight (MW), the absorption potential of the source substance can be expected to be slightly higher than that of the target substance, indicating that the source substance represents a worst case in terms of bioavailability. The constituents of the target and the source substances are predicted to be metabolized via similar pathways*".

8 You have provided the following information on the Substance and source substance to support your hypothesis:

- structural information
- similarity indices (Dice index) obtained using the OECD QSAR Toolbox v.4.3
- structural characteristics and mechanistic alerts obtained from the OECD QSAR Toolbox v.4.3
- prediction of the first metabolic reaction (ester hydrolysis) using the OECD QSAR Toolbox v.4.3
- information on physicochemical properties
- data on acute toxicity, skin irritation, eye irritation, skin sensitisation and gene mutation in bacteria on the Substance and the source substance, as well as repeated dose toxicity studies on the source substance.

9 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

10 Specifically, your read across hypothesis is based on two arguments. First you assume that your Substance and the source substance have similar toxicological profile based on structural similarity of the main constituents and the formation of common biotransformation products. Secondly, you consider that as bioavailability of the source substance is expected to be higher when compared to the Substance, therefore, the source substance is regarded as worst-case.

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

0.1.1.1. *Missing supporting information*

12 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

13 As indicated above, your read-across hypothesis is based on the assumption that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance, because of higher bioavailability. In this context, relevant, reliable and adequate information allowing to establish the rate of absorption, and compare the properties of the Substance and of the source substance(s) is necessary to confirm a conservative prediction of the properties of the Substance from the data on the source substance(s). Such information can be obtained, for example, from, toxicokinetic studies, bridging studies of comparable design and duration for the Substance and for the source substance(s).

14 In addition, for arguments involving bio transformation, supporting information should allow establishing the rate and extent of biotransformation to confirm the formation of the proposed common hydrolysis products needs to be provided.

15 In order to support your read-across hypothesis, you have provided the following information:

- Physico-chemical properties

16 You have provided a data matrix, comparing the physico-chemical properties of your Substance and the source substance. Both substances are liquids with comparable relative density, vapour pressure and flashpoint values but the Substance "has a higher log Kow

value and is less water soluble as compared to the source substance, suggesting that it is less bioavailable".

- Alert profiles using the QSAR Toolbox

17 Your Substance and the source substance have [redacted] as a common constituent and the following different key functional groups: acrylate, aryl, alkane, alcohol, carboxylic acid ester and ether groups. You have assessed the impact of the different functional groups using a set of physico-chemical and (abiotic and biotic) degradation properties structural characteristics and mechanistic alerts obtained from the QSAR Toolbox v3.4. Based on the QSAR Toolbox analysis you conclude that "the constituents of the target and source substances (concentration >[redacted]%) share similar structural alerts".

- Prediction of metabolic pathways using the QSAR Toolbox

18 In your justification document you have provided metabolic prediction, by using the OECD QSAR Toolbox v 4.3. metabolic simulators (in vivo rat metabolism simulator and rat liver S9 metabolism simulator) you have predicted that the constituents of the Substance and the source substance will undergo similar metabolic pathway (ester hydrolysis) and form acrylic acid as a common metabolite and the corresponding alcohol derivatives, as non-common metabolites. You further conclude that "*metabolites of significantly different toxicities will not be formed for the target and source substances*".

- Experimental studies

19 In order to support your claim that the Substance and source substance have similar properties for the endpoints under consideration in the read-across approach, you referred to their similarity in acute toxicity, irritation, skin sensitisation, and in vitro genotoxicity in bacteria.

20 As regards repeated dose toxicity studies, you have provided the following studies in your dossier, all performed with the source substance:

(i) Sub-chronic (90-day) repeated dose toxicity study in rat ([redacted], 2015);
(ii) Combined repeated dose toxicity study and Screening for reproductive/developmental toxicity test (2010);
(iii) Extended one-generation reproductive toxicity study (2019);
(iv) Pre-natal developmental toxicity study in rat (2015);
(v) Pre-natal developmental toxicity study in rabbit (2017).

21 You have not provided any studies on the Substance.

22 We have assessed the supporting information provided and identified the following issue(s):

- Physico-chemical properties

23 ECHA understands that you use the information on the physico-chemical properties of the substances to support your hypothesis that the absorption potential of the source substance is expected to be "slightly higher" than those of the Substance, therefore the source substance represents a worst case in terms of bioavailability.

24 ECHA notes that the information on physico-chemical properties on its own is insufficient to conclude on the toxicokinetic behaviour, in this case on absorption rate of the Substance and the source substance. You have not provided any experimental toxicokinetic data neither with the Substance nor with the source substance to support your claim for lower bioavailability of the Substance. Without such information, it is not possible to assess and compare the quantitative systemic exposure of the test organism and confirm your hypothesis of worst case for bioavailability.

- Alert profiles using the QSAR toolbox

25 There are structural differences between your Substance and the source substance. While the similarity in presence or absence of structural alerts may indicate that the differences do not influence the reactivity of the substance e.g. on the protein or DNA, ECHA notes that this information cannot serve as supporting information, to confirm the similar toxicological profile for mutagenicity, repeated dose toxicity, reproductive and developmental toxicity. In fact, the complexity of the systemic interactions and the reproductive process and the large number of targets/mechanisms associated with those broad areas of toxicity is not covered by computational tools.

26 The structural alerts reported in the justification document may indicate similarity in properties covered by the alerts. However, due to the complexity of the various mechanisms involved in mutagenicity, repeated dose toxicity, reproductive and developmental toxicity these profilers are by no means conclusive for these aspects of toxicity. Therefore, they can not be used, on their own, to compare the properties of the Substance and the source substance.

- Prediction of metabolic pathways using the QSAR Toolbox

27 ECHA notes that while the predicted ester hydrolysis is likely to be the primary metabolic pathway for both substances, you have not provided any experimental data to establish the rate and extent of biotransformation of the different constituents of the Substance and of the source substance.

28 Furthermore, you state that "metabolites of significantly different toxicities will not be formed for the target and source substances". However, you have not provided any information to support this statement.

29 Based on the above, you have not provided sufficient supporting information to scientifically justify your argument on common biotransformation and formation of metabolites with similar toxicological profile from the Substance and the source substance, which is integral part of your read-across hypothesis.

- Experimental studies

30 Firstly, you consider that the above mentioned studies ((i) to (v)) allow to compare the systemic, reproductive and developmental properties of the Substance with the source substance. While these studies provide relevant information on the properties of the source substance, ECHA notes that you did not provide any experimental data, in particular bridging studies of comparable design and duration for the Substance.

31 In the absence of such information it is not possible to compare the properties of the Substance and of the source substance and to confirm your hypothesis.

32 Secondly, while the information on acute toxicity, irritation, skin sensitisation, and in vitro genotoxicity in bacteria of the Substance and the source substance may provide support that the substances have similar properties for these toxicological properties, these studies do not inform on the genotoxicity in mammalian cells, sexual function, fertility and developmental properties of the Substance and source substance.

33 Therefore, this information does not provide relevant information for the Substance and of the source substance to support your read-across hypothesis for the information requirements you attempt to adapt.

34 Based on above, the available data set does not provide adequate supporting information to support your claim of similarity in toxicological properties. Consequently, no reliable comparison of the properties of the Substance and the source substance can be made.

0.1.1.2. *Adequacy and reliability of source studies*

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

a. be adequate for the purpose of classification and labelling and/or risk assessment;

b. have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);

c. cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

36 Specific reasons why the studies on the source substance do not meet these criteria are explained further below under the applicable information requirement sections 5. 6 and 7

37 Therefore, no reliable predictions can be made for these information requirements.

0.1.2. *Conclusions on the read-across approach*

38 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substances. Therefore, the read-across approaches do not comply with the general rules as set out in Annex XI, Section 1.5.

39 In your comments to the draft decision you agree with ECHA's conclusion that the read-across approach is not adequately supported and you express your intention to make it more robust by performing additional tests.

40 In order to provide evidence that the Substance and the source substance have a similar toxicological profile, you proposed a testing strategy relying on the generation of additional supporting information, as follows: as a first step, you intend to perform (i) combined screening for reproductive/developmental toxicity study with the Substance; (ii) *in vitro* absorption studies using Caco2 cell and (iii) *in vitro* metabolism studies, performed with both the Substance an the source substance. You consider that the new information, together with the outcome of the already existing OECD 422-study with DGEBADA, will allow you to stregthen the read-across hypothesis for sub-chronic (90-day) toxicity and prenatal developmental toxicity.

41 ECHA acknowledges your intention to improve the information on the toxicological profile of the Substance and to refine the read-across approach. As indicated in your comments, this strategy relies essentially on data which is yet to be generated, therefore no conclusion on the compliance can currently be made.

Reasons related to the information under Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates

42 Short-term toxicity testing on aquatic invertebrates is an information requirement under Column 1 of Annex VII to REACH (Section 9.1.1.). However, long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

1.1. *Triggering of the information requirement*

43 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

44 In the provided OECD TG 105 (2004), the saturation concentration of the Substance in water was determined to be $<7 \times 10^{-3}$ mg/L, hence below 1 mg/L.

45 Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

1.2. *Information provided*

46 You have provided a short-term toxicity study (OECD TG 202) but no information on long-term toxicity on aquatic invertebrates for the Substance.

1.3. *Assessment of the information provided*

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

48 In the absence of information on long-term toxicity on aquatic invertebrates, this information requirement is not fulfilled.

49 The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Request 8.

Reasons related to the information under Annex VIII of REACH

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

50 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..

2.1. *Information provided*

51 You have adapted this information requirement by using Annex VIII, Section 8.4.2., Column 2. To support the adaptation, you have provided the following information:

(i) A justification under section 7.6.1. of IUCLID stating that "*an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study does not need to be conducted because adequate data from an in vivo cytogenicity test are available*"

(ii) An *in vivo* mammalian erythrocyte micronucleus test (2007) with the analogue substance DGEBADA (EC 500-130-2)

2.2. *Assessment of the information provided*

2.2.1. *The provided adaptation does not meet the criteria of Annex VIII, Section 8.4.2., Column 2*

52 Under Annex VIII, Section 8.4.2., Column 2, the study usually does not need to be conducted "*if adequate data from an in vivo cytogenicity test are available*". The Guidance on IRs and CSA, Section R.7.7.6.3 and Table R.7.7–3 clarifies that the *in vivo* somatic cell cytogenicity test must be either a micronucleus test or a chromosomal aberration test, performed according to the OECD TG 474 or 475, respectively.

53 The study (ii) provided is described as *in vivo* mammalian erythrocyte micronucleus test, performed with an analogue substance.

54 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

55 Therefore, the column 2 criteria are not met and your adaptation is rejected.

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

2.3. *Specification of the study design*

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

58 In your comments to the draft decision you agree to perform the requested study.

3. In vitro gene mutation study in mammalian cells

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

3.1. *Triggering of the information requirement*

60 Your dossier contains (I) a negative result for *in vitro* gene mutation study in bacteria and (II) an adaptation for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study.

61 The *in vivo* micronucleus study provided in the dossier is rejected for the reasons provided in request 2

62 The result of the request 2 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.

63 Consequently, you are required to provide information for this information requirement, if the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provides a negative result..

3.2. *Information provided*

64 You have adapted this information requirement by using a Grouping of substances and read-across approach based on the following experimental data from the analogue substance DGEBADA (EC 500-130-2): an in vitro gene mutation study in mammalian cells (2010).

3.3. *Assessment of the information provided*

65 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

66 Therefore, the information requirement is not fulfilled.

3.4. *Specification of the study design*

67 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.

68 In your comments to the draft decision you agree to perform the requested study.

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

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

4.1. *Information provided*

70 You have adapted this information requirement by using a Grouping of substances and read-across approach based on the following experimental data from the analogue substance DGEBADA (EC 500-130-2):

(i) A sub-chronic (90-day) repeated dose toxicity study (2015);

(ii) Combined repeated dose toxicity study and Screening for reproductive/developmental toxicity test (2010).

4.2. *Assessment of the information provided*

4.2.1. *Read-across adaptation rejected*

71 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

72 Therefore, the information requirement is not fulfilled.

73 Your comments on the draft decision are addressed in Section 0.1.

4.3. *Specification of the study design*

74 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see information requirement section 6). According to Annex VIII, Section 8.6.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not therefore need to be conducted.

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

5. Screening for reproductive/developmental toxicity

76 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1., if there is no evidence from analogue substances, QSAR or in vitro methods that the substance may be a developmental toxicant.

5.1. *Information provided*

77 You have adapted this information requirement by using a Grouping of substances and read-across approach based on the following experimental data from the analogue substance DGEBADA (EC 500-130-2):

(i) Combined repeated dose toxicity study and Screening for reproductive/developmental toxicity test (2010);

(ii) Extended one-generation reproductive toxicity study (2019).

5.2. *Assessment of the information provided*

5.2.1. *Read-across adaptation rejected*

78 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

79 In addition, ECHA identified endpoint-specific issue(s) addressed below:

5.2.2. *Source study (ii) not adequate for the information requirement*

80 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, the following specifications must be met:

a) the highest dose level aims to induce toxicity or aims to reach the limit dose.

81 The study (ii) is described as a Extended one-generation reproductive toxicity study.

82 However, the following specifications are not according to the requirements of EU B.63/OECD TG 421 or EU B.64/OECD TG 422:

a) the highest dose levels tested was 200 mg/kg/day (i.e., below the limit dose of the OECD TG 422) and no adverse effect were observed. In addition, ECHA notes that there are OECD TG 422 and 414 studies available which show absence of adverse effects in parental animals and offspring up to the top dose of 900 and 1000 mg/kg bw/day, respectively. These studies are valuable in the context of dose selection to demonstrate the tolerable doses by parental animals and offspring. The results of the OECD TG 422 and 414 studies suggest that pregnant and paternal animals seem to tolerate well doses at around 1000 mg/kg bw/day.

83 Therefore, the study (ii) does not provide an adequate and reliable coverage of the key parameter(s) addressed by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422 and this study is not an adequate basis for your read-across predictions.

84 Based on the above, the information requirement is not fulfilled.

5.3. *Specification of the study design*

85 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.

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

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

88 In your comments to the draft decision you agree to perform the requested test.

Reasons related to the information under Annex IX of REACH

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

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

6.1. *Information provided*

90 You have adapted this information requirement by using a Grouping of substances and read-across approach based on the following experimental data from the analogue substance DGEBADA (EC 500-130-2):

(i) A sub-chronic (90-day) repeated dose toxicity study (2015).

6.2. *Assessment of the information provided*

6.2.1. Read-across adaptation rejected

91 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

92 Based on the above, the information requirement is not fulfilled.

93 Your comments on the draft decision are addressed in Section 0.1.

6.3. Specification of the study design

94 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.

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

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

7. Pre-natal developmental toxicity study in one species

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

7.1. *Information provided*

98 You have adapted this information requirement by using a Grouping of substances and read-across approach based on the following experimental data from the analogue substance DGEBADA (EC: 500-130-2):

(i) A prenatal developmental toxicity study in rat (2015)

(ii) A prenatal developmental toxicity study in rabbit (2017)

(iii) Combined repeated dose toxicity study and screening for reproductive/developmental toxicity test (2010)

7.2. *Assessment of the information provided*

7.2.1. *Read-across adaptation rejected*

99 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

7.2.2. *Source study (iii) not adequate for the information requirement*

100 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 414. Therefore, the following specifications must be met:

a) at least 20 female animals with implantation sites are included for each test and control group;
b) the dams are examined for any structural abnormalities, weight and histopathology of the thyroid gland, thyroid hormone measurements, gravid uterus weight, and uterine content;
c) the foetuses are examined for body weight, number and percent of live and dead foetuses and resorptions, sex ratio, external, skeletal and soft tissue alterations (variations and malformations), measurement of anogenital distance in all live rodent foetuses.

101 The study (iii) is described as a Combined repeated dose toxicity study and screening for reproductive/developmental toxicity test.

102 However, the following specifications are not according to the requirements of the OECD TG 414:

a) only 10 females were included in each test and control group;
b) data on the examination of the dams, including incidence and severity, are missing; In particular, the following investigations are missing: weight and histopathology of the thyroid gland, thyroid hormone measurements, gravid uterus weight, and uterine content
c) data on the examination of the foetuses, including incidence and severity, are missing; In particular, the following investigations are missing: external, skeletal and soft tissue alterations (variations and malformations).

103 Based on the above, the study does not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 414 and this study is not an adequate basis for your read-across predictions.

104 Therefore, the information requirement is not fulfilled.

105 Your comments on the draft decision are addressed in Section 0.1.

7.3. *Specification of the study design*

106 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species.

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

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

8. Long-term toxicity testing on aquatic invertebrates

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

8.1. *Information provided*

110 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following information:

(i) *" In accordance with column 2 of REACH Annex IX, the study shall be proposed if the exposure and risk assessments indicate the need to investigate further the effects on aquatic organisms. As specified in ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b, Section R.7.8.5.3., a risk is indicated by the Chemical Safety Assessment (CSA) for substances with log Kow > 3 (to indicate bioaccumulation potential) and a PEClocal or PECregional > 1/100th of the water solubility. Therefore, given the low bioaccumulation assessment for the different constituents of the test substance (see section 4.3.3 of the CSR) together with PECfresh water and marine water values for all scenarios as below 1/100th of the water solubility (i.e., <0.007 µg/L), all the supported uses are assessed to be safe and no further long-term testing is proposed for the aquatic compartment."*

8.2. *Assessment of the information provided*

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

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

112 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).

113 Your adaptation is therefore rejected and the information requirement is not fulfilled.

8.3. *Study design and test specifications*

114 The Substance is difficult to test due to the low water solubility (< 0.07 mg/L). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare

test solutions was adequate to maximise the concentration of the Substance in the test solution.

115 In your comments to the draft decision you agree to perform the requested study.

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 a long term study testing on fish (Annex IX, section 9.1.6) is not addressed in this decision. This information requirement 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; this is due to the fact that the results from the 90-day study is needed for the design of the long-term toxicity testing on fish.

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 23 August 2021.

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

ECHA took into account your comments did not amend the request(s).

Deadline to submit the requested information in this decision

In the comments on the draft decision, you requested an extension of the deadline from 24 to 36 months from the date of adoption of the decision. To justify the additional time needed for aquatic toxicity testing, you stated that due to the low water solubility and UVCB nature of the Substance, you "*may need several pre-tests to define the right set-up of the study design. Also developing a good and reliable analytical method will be a challenge, and hence time consuming*". In addition, you pointed out to the limited capacity of the testing laboratories and provided information from three CROs indicating that, based on the current capacity of the laboratory, 36 months are needed to perform and submit the studies.

Based on the documentary evidence provided, ECHA has agreed with your request for a deadline extension and has extended the deadline to 36 months.

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

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

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

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

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

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

Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

a) the variation in compositions reported by all members of the joint submission,
b) the boundary composition(s) of the Substance,
c) 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.

Information on the Test Material needed in the updated dossier

a) 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.
b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using

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

the appropriate analytical methods,

With that detailed information, ECHA can confirm 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 (https://echa.europa.eu/manuals).

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

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