EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 12 February 2021

Addressees
Registrant(s) of EpoxyResins_240-260-4 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
19 September 2017

Registered substance subject to this decision ("the Substance")
Substance name: Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane (1:2)
EC number: 618-939-5
CAS number: 933999-84-9

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of **20 May 2024**.

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

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

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

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

1. 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)

2. Same in vivo genotoxicity study as request C.1 (triggered by Annex VIII, Section 8.4., column 2)

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

1. In vivo genotoxicity study to be selected according to the following scenarios:

   a. If the test results of request B.1 are negative:

   In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum

   OR

   Transgenic rodent somatic and germ cell gene mutation assays (Annex IX, Section

8.4., column 2; test method OECD TG 488 from 2020[1]) in transgenic mice or rats, oral route on the following tissues: liver, glandular stomach, with the Substance; germ cells and duodenum must be harvested and stored for up to 5 years. The duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.

b. If the test results of request B.1 are positive:

In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method OECD TG 489) combined with *in vivo* mammalian erythrocyte micronucleus test (test method: OECD TG 474) in rats, oral route. For the comet assay the following tissues shall be analysed: liver, glandular stomach and duodenum.

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

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

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

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

Reasons for the request(s) are explained in the following appendices:

- Appendices entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- 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.

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

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under

[1] The updated OECD TG 488, adopted on 26 June 2020, is available on OECD website at https://www.oecd-ilibrary.org/docserver/9789264203907-en.pdf?expires=1596539942&id=id&accname=guest&checksum=D552783C4CB0FC8045D04C88EFFBFA66.

Article 53 of REACH.

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[2] 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 A: Reasons to request information required under Annex VII of REACH

1. Growth inhibition study aquatic plants

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

You have adapted the standard information requirement by using a Qualitative or Quantitative structure-activity relationship ((Q)SAR) under Annex XI, Section 1.3.

In your dossier, you have provided a QSAR prediction on algae toxicity using the Danish National Food Institute (MultiCASE platform) model, MultiCASE v. 2005.

Annex XI, Section 1.3. states that the results obtained from valid QSAR models may be used instead of testing when the following cumulative conditions are met, in particular:

1. results are derived from a QSAR model whose scientific validity has been established;
2. the substance falls within the applicability domain of the QSAR model;
3. adequate and reliable documentation of the applied method is provided; and
4. the results are adequate for classification and labelling and/or risk assessment.

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

In your dossier you have provided a QMRF document and reported an estimated value of EC50 (48 h) = 23.1 mg/L. Also, you have provided a training set document (OECD Toolbox-training set). You have not provided the QPRF document of the prediction.

Based on the content of your dossier, the reported prediction cannot be used for the following reasons:

- The QPRF document is missing, therefore ECHA is not able to verify if the Substance falls within the applicability domain (criterion 2).
- Regarding the training set, the document contains only the structures and identifiers of a list of substances, however there is no information given on the experimental algae result values used as basis for the model; therefore criterion 3 is not met. Furthermore, based on the data in your dossier, the Substance is an UVCB and contains five constituents, however the prediction was based on only one constituent, and no justification was provided to explain the reasons for not considering the other constituents. Therefore, overall, no conclusion on the scientific validity and reliability of the prediction, and on the adequacy to provide information for the Substance can be made, and consequently the criteria 1 and 4 are not met.

Consequently the predictions are not adequate for classification and labelling and/or risk assessment.Therefore, your adaptation does not fulfil the criteria specified in Annex XI, Section 1.3. and is rejected.

Therefore, the information requirement is not fulfilled.

In the comments on the draft decision, you agree to perform the requested study to fulfil the information requirement.

Appendix B: Reasons to request information required under Annex VIII of REACH

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

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have provided a study in your dossier:

i. [redacted] (1990), conducted with the Substance according to OECD TG 474 and GLP.

You have also included a data waiver in your dossier with a justification referring to Section 8.4.2., Column 2, first indent, Annex VIII to REACH.

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

Under Section 8.4.2., Column 2, first indent, Annex VIII to REACH, the study may be omitted if "*adequate data from an in vivo cytogenicity test*" is available. ECHA Guidance R.7.7.3.1. clarifies that the *in vivo* study must be either a micronucleus test or a chromosomal aberration test, performed according to OECD TG 474 or 475, respectively[3].

For the data from an *in vivo* cytogenicity test to be considered adequate, the *in vivo* study you submitted has to meet the requirements of OECD TG 474, and the specifications/conditions of this test guideline include:

a) The study must include a minimum of three doses/groups of treated animals, as well as a negative control group and a positive control group.
b) In order to provide a clear negative outcome, the data available must show that "*bone marrow exposure to the test Substance occurred*".

The reported data for the *in vivo* study you submitted did not include:

a) the appropriate number of doses, as only one dose was studied;
b) a demonstration that the systemic or target tissue (bone marrow) exposure to the Substance or its metabolites.

The information provided does not cover key parameter(s) required by OECD TG 474.

Therefore, the requirements of Section 8.4.2., Column 2, first indent, Annex VIII to REACH are not met.

Study design

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.

In the comments on the draft decision, you agree to perform the requested study to fulfil the information requirement.

[3] ECHA Guidance R.7a, Table R.7.7-3, p.558

2. In vivo genotoxicity study to be selected according to the following scenarios:

a. If the test results of request B.1 are negative:

In vivo mammalian alkaline comet assay OR Transgenic rodent somatic and germ cell gene mutation assay

b. If the test results of request B.1 are positive:

In vivo mammalian alkaline comet assay combined with *in vivo* mammalian erythrocyte micronucleus test

Under Annex VIII, Section 8.4, Column 2 of REACH, the performance of an appropriate *in vivo* somatic cell genotoxicity study must be considered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII.

The ECHA guidance R.7a states that following a positive result in an *in vitro* test, "*adequately conducted somatic cell in vivo testing is required to ascertain if this potential can be expressed in vivo. In cases where it can be sufficiently deduced that a positive in vitro finding is not relevant for in vivo situations (e.g. due to the effect of the test substances on pH or cell viability, in vitro-specific metabolism: see also Section R.7.7.4.1), or where a clear threshold mechanism coming into play only at high concentrations that will not be reached in vivo has been identified (e.g. damage to non-DNA targets at high concentrations), in vivo testing will not be necessary.*"

Your dossier contains positive results for the *in vitro* gene mutation study in bacteria ([redacted] 1987) which raise the concern for gene mutation.

Moreover, you did not provide any consideration explaining that the genotoxic potential of the substance cannot be expressed *in vivo*, based e.g. on lack of relevance for *in vivo* situations or the existence of threshold mechanism.

ECHA considers that an appropriate *in vivo* follow up mutagenicity study is necessary to address the concern identified *in vitro*.

For the assessment of the *in vivo* studies submitted in your dossier and the selection of the appropriate test and its design, we refer to the reasons given in Appendix C, Section 1.

In the comments on the draft decision, you agree to perform a study to fulfil the information requirement.

Appendix C: Reasons to request information required under Annex IX of REACH

1. **In vivo genotoxicity study to be selected according to the following scenarios:**

   a. If the test results of request B.1 are negative:

   In vivo mammalian alkaline comet assay OR Transgenic rodent somatic and germ cell gene mutation assay

   b. If the test results of request B.1 are positive:

   In vivo mammalian alkaline comet assay combined with *in vivo* mammalian erythrocyte micronucleus test

Under Annex IX, Section 8.4, column 2 of REACH, the information requirement for an appropriate *in vivo* somatic cell genotoxicity study is triggered if 1) there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and 2) there are no appropriate results already available from an *in vivo* somatic cell genotoxicity study.

In relation to the first condition, your dossier contains positive results for the *in vitro* gene mutation study in bacteria which raise the concern for gene mutation.

In relation to the second condition, your dossier contains the following *in vivo* studies:

i. [redacted] (1990), conducted with the Substance according to OECD TG 474
ii. [redacted] 1994), conducted with the Substance according to OECD TG 486.

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

ECHA Guidance R.7a clarifies that in order to justify that an *in vivo* somatic cell genotoxicity study does not need to be performed in accordance with Annex IX, Section 8.4, column 2, the results of the available *in vivo* study must address the specific concern raised by the *in vitro* positive result.

However, the *in vivo* study (i) provided is not addressing the gene mutation concern raised by the *in vitro* data. Study (i) addresses a chromosomal aberration concern. Moreover, as explained under section B.1, study (i) does not cover all key parameter(s) required by OECD TG 474.

Study (ii), again, does not give adequate information, as required by OECD TG 488, because it is an Unscheduled DNA Synthesis (UDS) assay which provides an indication of induced damage to DNA followed by DNA repair, measured as unscheduled DNA synthesis, but does not provide direct evidence of mutation as the Transgenic Rodent (TGR) Somatic and Germ Cell Gene Mutation Assay (OECD TG 488). As indicated in the ECHA Guidance R.7.7.6.3, a negative result in a UDS assay alone is not a proof that a substance does not induce gene mutations.

The provided *in vivo* tests are not appropriate and/or not adequate to address the concern identified by the *in vitro* gene mutation study in bacteria. Therefore, the conditions set out in Annex IX, Section 8.4, column 2 are met and the information requirement for an appropriate *in vivo* somatic cell genotoxicity study is triggered.

Test selection

According to the ECHA Guidance Chapter R.7a[4], the transgenic rodent somatic and germ cell gene mutation assay ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a *positive in vitro* result on gene mutation.

This decision, however, also requests an *in vitro* test under Annex VIII Section 8.4.2 (see section 1 of Appendix B), which may raise a concern for chromosomal aberration in case of positive results. This concern can be addressed by the comet assay, but not by the TGR assay.

In case there is a concern for both gene mutation and chromosomal aberration, the comet assay can be combined with the *in vivo* mammalian erythrocyte micronucleus test ("MN test", OECD TG 474) into a single study. The MN test is a mutagenicity test that provides evidence on *in vivo* chromosomal mutagenicity, as the study detects both structural and numerical chromosomal aberrations. The combined study can help reduce the number of tests performed and the number of animals used while addressing both chromosomal aberration and gene mutation.

Therefore it is appropriate to wait for the results of the *in vitro* test requested under B.1 and, depending on these results, to conduct either a) the TGR or comet assay, or b) the comet assay combined with the MN test. The deadline set in this decision allows for sequential testing.

Test design

a) TGR or comet assay

In case you decide to perform the comet assay according to the test method OECD TG 489, the test must be performed in rats. Having considered the anticipated routes of human exposure and the need for adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

In case the TGR assay is appropriate and you decide to conduct this test, according to the test method OECD TG 488, the test must be performed in transgenic mice or rats and the test substance is usually administered orally.

Based on the recent update of OECD TG 488, you are requested to follow the new 28+28d regimen, as it permits the testing of mutations in somatic tissues as well as in tubule germ cells from the same animals. This updated version provides for a transitional period for the new version. However, ECHA is aware that testing according to the updated OECD TG is already available from CROs and the new study design would provide meaningful germ cell data, so this decision requires the application of the new version.

[4] ECHA Guidance Chapter R.7a, Section R.7.7.6.3

According to the test method OECD TG 488, the test must be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, glandular stomach and duodenum as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum must be stored (at or below −70 °C) until the analysis of liver and glandular stomach is completed; the duodenum must then be analysed only if the results obtained for the glandular stomach and for the liver are negative or inconclusive.

b) Comet assay combined with the MN test

In case there is a concern for both gene mutation and chromosomal aberration, the combined test (OECD TG 489 and OECD TG 474) must be performed in rats. Having considered the anticipated routes of human exposure and the need for adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

The combination of OECD TGs 489 and 474 should not impair the validity of and the results from each individual study. Careful consideration should be given to the dosing, and tissue sampling for comet analysis alongside the requirements of tissue sampling for the mammalian erythrocyte micronucleus test (see OECD TG 489, e.g. Bowen *et al.* 2011[5]).

Germ cells

A subsequent germ cell genotoxicity study (TGR/OECD TG 488, or CA on spermatogonia/OECD TG 483) may still be required under Annex IX/X of REACH, in case 1) an *in vivo* genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity.

Therefore, depending on the result of B.1, if you perform either the comet assay or the comet assay combined with the MN test, you may consider to collect the male gonadal cells from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, in accordance to Annex IX/X, Section 8.4., column 2, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment

[5] Bowen D.E. et al. 2011. Evaluation of a multi-endpoint assay in rats, combining the bone-marrow micronucleus test, the comet assay and the flow-cytometric peripheral blood micronucleus test. Mutation Research 722 7–19

of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

In case the TGR assay is appropriate and you decide to conduct this test, you must collect the male germ cells (from the seminiferous tubules) at the same time as the other tissues, in order to limit additional animal testing. According to the OECD 488, the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years (at or below −70 ºC). This duration is sufficient to allow you or ECHA, in accordance to Annex IX, Section 8.4., column 2, to decide on the need for assessment of mutation frequency in the collected germ cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

In the comments on the draft decision, you agree to perform a study to fulfil the information requirement. You state your intention to perform an OECD 488 TGR assay. Additionally, in your comments to the proposal for amendments (PfAs) submitted by one of the Member States Competent Authorities (MSCAs), you reiterate your preference to perform an OECD 488 TGR assay, nonetheless presented a workflow with conditional testing to be based on the results of requested *in vitro* chromosomal aberration study under B.1.

We reiterate that the selection of the appropriate *in vivo* study to be conducted should consider the results of the requested *in vitro* test under Annex VIII Section 8.4.2 (see section 1 of Appendix B) as this study may raise an additional concern for chromosomal aberration. Should this be the case, this concern and the concern on gene mutation can be addressed by the comet assay combined with the MN test study, whereas the TGR assay is not appropriate to follow-up on a concern on cytogenicity. If however there is no additional concern for chromosomal aberration, then you are only required to address the gene mutation concern by performing either a comet assay or a TGR assay and not both tests. The deadline set in this decision allows for sequential testing.

2. Long-term toxicity testing on aquatic invertebrates and fish

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

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

You have (i) adapted these information requirements according to Annex IX, Section 9.1, Column 2, based on the consideration that the chemical safety assessment does not indicate a need for further testing, and (ii) indicated in the comments on the draft decision an intention to adapt these information requirements according to Annex XI, Section 1.5 by a read-across approach.

ECHA has assessed the information and identified the following issue:

(i) Adaptation according to Annex IX, Section 9.1, Column 2

Under Section 9.1., Column 2, Annex IX to REACH, long-term toxicity on invertebrates and long-term toxicity on fish studies may be omitted if the Chemical Safety Assessment demonstrates that risks towards the aquatic compartment arising from the manufacture and use of the substance are controlled (Annex I, Section 0.1). The justification for this adaptation must be documented in the Chemical Safety Report (CSR) and include among others the

predicted no effect concentrations (PNEC) for the aquatic compartment which must be based among others on reliable information on the hazardous properties of the Substance on at least three trophic levels.

For the reasons explained under requests Appendix A, sections 1 and 2, your dossier does not include reliable hazard information for the Substance on at least three trophic levels.

Therefore, a reliable PNEC cannot be derived, consequently you have not demonstrated that the risks are adequately controlled (*i.e.* PEC < PNEC) and your adaptation is rejected.

(ii) Your considerations on an adaptation according to Annex XI, Section 1.5

In the comments on the draft decision you indicate your intention to adapt these information requirements by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

You have provided a read-across justification document in the comments on the draft decision.

You propose to read-across between the structurally similar substances, 1,4-butanediol, reaction product with 1-chloro-2,3-epoxypropane (BDDGE, EC No. 219-371-7) as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of ecotoxicological properties: *"both substances show similar results in the current aquatic studies, between 20 and 110 mg/L depending on the trophic level"*.

ECHA understands that you intend to predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

You indicate that you will perform the Long-term toxicity studies on fish and invertebrates on the source substance. In the absence of the source studies, the compliance of these studies or the read-across prediction cannot yet be assessed. Therefore, the data gap remains and the information requirement is not fulfilled.

Furthermore, based on the intentions and justification provided in the comments to the draft decisions the following shortcomings of the approach are noted.

Missing supporting information to compare properties of the substances

Annex XI, Section 1.5 of the REACH Regulation states that *"physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)"*. For this purpose *"it is important to provide supporting information to strengthen the rationale for the read-across"*[6]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).
As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

of the source substance(s) is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

In the read-across justification provided in the comments on the draft decision, you have included a data matrix where the following studies are listed:

	For the Substance	For the source substance
Short-term toxicity testing on aquatic invertebrates	OECD 202, EC50 (48h): 47 mg/L	OECD 203, EC50 (24 h): 75 mg/L test mat. (nominal); indicating that exposure time was only 24 h and analytical verification was lacking
Growth inhibition study on algae	Study will be performed	OECD 201, EL50 (72 h): 110 mg/L test mat. (nominal, biomass), EL50 (72h): >160 mg/L test mat. (nominal, growth rate)
Short-term toxicity testing on fish	OECD 203, LC50 (96h): ca.30 mg/L, and OECD 203, LC50 (96h): ca.17.1 - ca.30.9 mg/L	OECD 203, non-GLP: LC50 (96 h): 24 mg/L
Activated Sludge, Respiration Inhibition Test	OECD 209, IC50 (3 h): >100 mg/L	OECD 209, IC50 (3 h): > 100 mg/L
Long-term toxicity testing on invertebrates	Study results will be read across from BDDGE	Study (OECD 211) will be performed pending the results of the acute aquatic studies.
Long-term toxicity testing on fish	Study results will be read across from BDDGE	Study (OECD 210) will be performed pending the results of the acute aquatic studies.

You note shortcomings in the short-term toxicity study on invertebrates for the source substance and a reliable growth inhibition study on algae for the Substance is not yet available (as discussed in Appendix A.2). No information is currently provided on long-term toxicity to fish and invertebrates for the substances.

Therefore, only the short-term toxicity to fish and activated sludge, respiration inhibition can be compared between the Substance and the source substance by the information provided in the justification. These data in the data matrix suggests that the substances have similar toxicity in the endpoints measured in the tests.

However, you have not provided any evidence or justification how this information is relevant for the prediction of toxicity to early life stages of fish (i.e. stage of embryonic development, hatching, abnormal appearance and behaviour, length and weight) and aquatic invertebrates (reproductive output of Daphnia) as investigated in the requested studies according to OECD TG 211 and 210. In the absence of adequate information allowing to compare the properties of the Substance and of the source substance it cannot be confirmed that both substances cause the same type of effects. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Appendix D: Reasons to request information required under Annex X of REACH

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

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

You have not provided any study in a second species.

You have provided a study conducted with the Substance according to the test guideline OECD TG 414 (Prenatal Developmental Toxicity Study) in the rat as a first species [redacted] 2017). Furthermore you have included a data waiver with a justification referring to Annex X, Section 8.7., Column 2, third indent, as well as the studies [redacted] 2010 (OECD 422) and [redacted] 2017 (OECD 408, OECD 414) as supporting information.

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

According to Annex X, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, namely:

- that there is no evidence of toxicity seen in any of the tests available; and
- that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
- that there is no or no significant human exposure.

In your adaptation, you have not substantiated your claim on no toxicity. In your testing Proposal justification for the other reproductive toxicity information requirement, the extended one-generation reproductive toxicity study, you moreover state that the Substance "*is not a substance of low toxicological activity, systemic absorption of HDDGE does occur, and there is potential human exposure. The column 2 specific adaption rules are not met and the studies must be conducted.*"
In addition, you have not provided any toxicokinetic data to show that there is no systemic absorption. Furthermore, the uses of the Substance (such as PROCs 7, 10, 11, 13, 19) indicate that there is human exposure.

Based on the above, the information you provided do not fulfil the information requirement.

Information on study design

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred species. The test in the first species was carried out by using a rodent species (rat). Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

The study shall be performed with oral[7] administration of the Substance.

In the comments, you present a strategy relying on the generation of additional supporting information on the Substance and on the analogue substance 1,4-bis(2,3-epoxypropoxy)butane (BDDGE, EC 219-371-7), i.e. performing the preliminary study for PNDT in a second species (rabbit) on both substances. Based on the information obtained from these studies, and taking into account the results of an OECD 414 study in a first species yet to be conducted on BDDGE after being requested by ECHA in a separate compliance check decision, and the available data from an OECD 414 study on HDDGE, you will decide on

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

whether the PNDT study in the second species should be performed on HDDGE, or BDDGE and read across to HDDGE.

As this strategy relies essentially on data which is yet to be generated, no conclusion on the compliance can currently be made. Should you decide to pursue the strategy presented in your comments, ECHA will assess its compliance in the follow-up to the dossier evaluation.

Appendix E: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. 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[8].

B. 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 identify all the constituents as far as possible as well as their concentration (OECD GLP (ENV/MC/CHEM(98)16) and EU Tests Methods Regulation (EU) 440/2008 (Note, Annex). Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,
   - The reported composition must also include other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[9].

[8] https://echa.europa.eu/practical-guides
[9] https://echa.europa.eu/manuals

Appendix F: General recommendations when conducting and reporting new tests for REACH purposes

Testing strategy for aquatic toxicity testing

You are advised to consult ECHA Guidance R.7b, (Section R.7.8.5) which describes the Integrated Testing Strategy, to determine the sequence of aquatic toxicity tests and testing needed.

Appendix G: Procedure

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 8 January 2020.

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

ECHA took your comments into account. On this basis, the original request on "Short-term toxicity testing on aquatic invertebrates" was removed. ECHA did not amend the other request(s) or the deadline.

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-73 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix H: List of references - ECHA Guidance[10] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[11]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[11]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

[10] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[11] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

OECD Guidance documents[12]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

[12] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix I: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

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