EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 12 February 2021

Addressees
Registrant(s) of EpoxyResins_219-371-7 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
31/01/2020

Registered substance subject to this decision ("the Substance")
Substance name: 1,4-bis(2,3-epoxypropoxy)butane
EC number: 219-371-7
CAS number: 2425-79-8

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 in B.1 below by ***20 May 2022*** and all other information listed below by ***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. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

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

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

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

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

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

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

1. In vivo mammalian alkaline comet assay (Annex X, 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 X, Section 8.4., column 2; test method: OECD TG 488 from 2020[1]), in rats, oral route, on the following tissues: liver and glandular stomach; germ cells and duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.

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

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

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII, IX 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 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.

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 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".

[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.

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 on Reasons common to several requests

Assessment of your read-across approach under Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 appendices.

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 (addressed under 'Assessment of prediction(s)').

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

A. Predictions for toxicological properties

You have provided read-across justification documents in different sections of IUCLID.

You read across between the structurally similar substance Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane EC No. 618-939-5 (CAS No. 933999-84-9) as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: *"Both do share the same functional groups (glycidyl ethers) and only do distinguish by the length of the alkyl chain between the two glycidyl ether functions, whereas both alkyl chains are even numbered. (4 and 6). Their physical properties are very similar [...], but also their known toxicological properties are absolutely comparable, justifying the use of available data from reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane (HDDGE) to predict toxicity"* of the Substance; *"The two substances (source and target) do share the same functional group, and these functional groups do dominate any toxic effects (e.g. irritation of skin, eyes and mucous membranes), whereas the central alkyl moiety (butylene or hexylene, respectively) is toxicologically rather inactive."*

ECHA understands that you predict the properties of the Substance using a read-across

[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[4] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[5] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

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.

ECHA notes the following shortcoming(s) with regards to prediction(s) of toxicological properties.

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 in your dossier, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both 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 order to support your claim that your Substance and source substance have similar properties for the endpoints under consideration in the read-across approach, you have provided a data matrix which includes data on physico-chemical and toxicological endpoints for the Substance and the source substance. You refer to their acute toxicity, skin irritation, eye irritation properties, genotoxicity in vitro (Ames), genotoxicity in vivo and sub-acute oral repeated dose toxicity, stating that "*The two substances (source and target) do share the same functional group, and these functional groups do dominate any toxic effects (e.g. irritation of skin, eyes and mucous membranes), whereas the central alkyl moiety (butylene or hexylene, respectively) is toxicologically rather inactive.*" and "*This is supported by the strong similarities in acute and sub-acute toxicity data as well as genotoxicity data on both substances, clearly showing very similar and almost identical behaviour in biota*".

Whilst this data set suggests that the substances may have similar properties for the toxicological endpoints listed above, these studies do not inform in particular on the developmental and reproductive toxicity properties of the target and source substances. Accordingly, these information are not considered as relevant to support prediction of all the endpoints under consideration.

In the absence of such information, you have not established that the Substance and of the source substance are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

B. Conclusions on the read-across approach

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

[6] ECHA Guidance R.6, Section R.6.2.2.1.f

Appendix A: Reasons to request information required under Annex VII of REACH

1. Short-term toxicity testing on aquatic invertebrates

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

You have provided a key study with the Substance according to OECD TG 202.

ECHA has assessed this information and identified the following issues:

To fulfil the information requirement, a study must comply with OECD TG 202 (Article 13(3) of REACH). Therefore, the following requirements must be met:

- the test duration is 48 hours or longer;
- the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
- the effect values can only be based on nominal or measured initial concentration if evidence is provided that the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1).
- the number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation;
- the percentage of immobilised daphnids is ≤ 10% at the end of the test in the controls

Your registration dossier provides an OECD TG 202 study showing the following:

- The test duration is 24 hours;
- the concentrations of the test material in the test solutions were not measured;
- you have not provided the tabulated data on the number of immobilised daphnids after 24 and 48 hours for the control.

you have indicated that the validity criteria of OECD TG 202 have been fulfilled.

Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results of the provided study according to OECD TG 202. More, specifically the test duration was 24 hours instead 48 hours, therefore the sensitivity and the reliability of the study could be impacted. In addition there is no analytical monitoring of the test concentrations and no other evidence that the Substance is stable throughout the exposure duration.

Furthermore, the reporting of the study in both studies is not sufficient to conduct an independent assessment of its reliability and validity. No information on the immobilisation in the control has been provided , therefore you have not demonstrated that the percentage of immobilised daphnids is ≤ 10% at the end of the test. Consequently, you have not demonstrated that the validity criteria have been fulfilled.

Therefore, the study does not meet the requirement listed above.

In the comments on the draft decision, you agree that the study provided does not meet the current standards of an OECD TG 202 study. Instead of performing a new OECD TG 202 study as requested, you propose to perform the other requested aquatic toxicity studies, i.e. OECD TG 211 and OECD TG 210 studies (ECHA requests also these studies; see Appendix B, Sections 3 and 4, for the reasons). You consider that the range finding study from OECD TG 211 would meet the information requirement of Short-term toxicity on aquatic invertebrates.

REACH Annex VII section 9.1.1 column 2 specifies that the short-term toxicity study does not need to be conducted if a long-term aquatic toxicity study on invertebrates is available. But at present no long-term toxicity study on aquatic invertebrates is yet provided in the IUCLID dossier. You are still responsible to provide the information in an update of your registration, by the deadline set in this decision. Only then ECHA will be able to assess the compliance in the follow-up to the dossier evaluation.

On the basis of the above, the information requirement is not fulfilled.

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

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

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided the following information for this endpoint in your dossier:

i. an adaptation according to Annex XI, Section 1.5. to REACH (read-across) by providing the following study: [redacted] 2017, conducted with the analogue substance 2,2'-[hexane-1,6-diylbis(oxymethylene)]dioxirane EC No. 618-939-5 (CAS No. 933999-84-9) according to OECD TG 408

ii. [redacted] 2010, conducted with the Substance according to OECD TG 407.

We have assessed this information and identified the issues explained in the draft decision notified to you.

Firstly, ECHA identified an incompliance of the information in the evaluated dossier and read-across justification regarding the characterisation of the source substance (UVCB).

In your comments you accepted this shortcoming and you provided an updated read-across justification in your comments. You have clarified the composition of the source substance and the compositional comparison of source and target in order to show that the read-across reliability is not affected by different components of the two substances and their concentrations.

ECHA agrees that the submitted information is sufficient to support the read-across justification regarding the aspect of characterisation of source and target.

Secondly, in your comments on the draft decision you also clarified that you were not intending to use the study ii. above to fulfil the information requirement, but to serve as bridging information, together with a sub-acute toxicity study (OECD TG 422) available for the source substance.

This information is relevant to support the read-across hypothesis for the read-across adaptation using the analogue substance Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane (EC 618-939-5) as source substance. This resolves the issue described in the Appendix on Reasons common to several requests above for this endpoint.

To conclude, the information you have provided in your comments addresses the incompliances identified for this information requirement. However, as the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision. Only then ECHA will be able confirm the acceptance of the read-across adaptation in the follow-up to the dossier evaluation.

Information on the design of the study to be performed

Referring to 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, because although the information indicate that human exposure to the Substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route are low.

Therefore, if the information requirement should not be adapted by way of amending the adaptation approach in your dossier in line with the information from your comments, the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

2. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have provided an adaptation according to Annex XI, Section 1.5. to REACH (read-across) by providing the following study: [redacted] 2017, conducted with the analogue substance Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane EC No. 618-939-5 (CAS No. 933999-84-9) according to OECD TG 414.

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

As explained in the Appendix on Reasons common to several requests, your adaptation based on Annex XI, Section 1.5. is rejected.

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

Information on the design of the study to be performed

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral administration of the Substance.

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

3. Long-term toxicity testing on aquatic invertebrates; and

4. Long-term toxicity testing on 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 adapted these information requirements according to Annex IX, Section 9.1, Column 2, based on the consideration that chemical safety assessment does not indicate a need for further testing.

ECHA assessed this information and identified the following issue:

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 it must include the predicted no effect concentrations (PNEC) for the aquatic compartment which must be based on, among

others, reliable information on the hazardous properties of the Substance on at least three trophic levels.

In your dossier you provided a PNEC value of 0.024 mg/L. This value was calculated based on the acute studies from the three trophic levels, you considered the LC50 fish (96h) as the lowest effect value. However, for the reasons explained under request A.1 the short term invertebrate study does not fulfill the information requierement according to the OECD TG 202. Therfeore 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.

Based on the above, the information requirements are not fulfilled.

In your comments on the draft decision you agree to perform the requested studies to fulfil these information requirements.

Study design

To fulfil the information requirement for the Substance for long-term toxicity testing on fish, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

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

1. In vivo mammalian alkaline comet assay; or Transgenic rodent somatic and germ cell gene mutation assays

Under Annex X, Section 8.4, column 2 of REACH, the information requirement for a second *in vivo* somatic cell genotoxicity study is triggered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII but depending on the quality and relevance of all the available data.

Your dossier contains positive results for the *in vitro* gene mutation study in bacteria and *in vitro* cytogenicity tests and *in vitro* gene mutation study in mammalian cells, which raise both concerns, i.e. gene mutation and chromosomal aberration.

Also, your dossier contains the following *in vivo* studies:

i. [redacted] 2010, key study, micronucleus assay, conducted with the Substance according to OECD 474
ii. [redacted] 1984, supporting study, micronucleus assay, conducted with the Substance, non-guideline
iii. [redacted] 1983, key study, sister chromatid exchange assay, conducted with the Substance, non-guideline.

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

The ECHA guidance R.7a[7] states that the second *in vivo* test is required "if *the in vitro* data show the substance to have potential to induce both gene and chromosome mutations and the first *in vivo* test has not addressed this comprehensively".

However, no data from an *in vivo* somatic cell genotoxicity study that addresses gene mutation is available in the dossier.

The provided *in vivo* tests are not sufficient to address both concerns.

Therefore the information requirement for a second *in vivo* somatic cell genotoxicity study is triggered.

Test selection

According to the ECHA Guidance Chapter R.7a[8], 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.

Test design

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.

[7] ECHA Guidance R.7a, Section R.7.7.6.3, p.570.
[8] ECHA Guidance R.7a, Section R.7.7.6.3

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 you decide to perform the TGR assay, 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 and 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.

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.

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 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, in case you decide to perform the comet assay, you may consider to collect the male gonadal cells collected 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 of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

Therefore, in case you decide to perform the TGR, 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 °C).

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 your comments you acknowledge the existing data gap to be filled and state your intention to fulfil the information requirement. You suggest an adaptation according to Annex XI, Section 1.5 using the analogue substance Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane (EC 618-939-5) as source for the *in vivo* somatic cell genotoxicity study. You refer to the strong similarity between the substances and the similar behaviour in existing *in vitro* and *in vivo* genotoxicity studies available for the Substance and the analogue substance as bridging information. You propose to perform an OECD TG 488 study in transgenic mice or rats with the analogue substance and read across to the Substance.

As this strategy relies on source study with the analogue as well as additional bridging *in vitro* study data (i.e. *in vitro* study requested in the decision for analogue substance), which is yet to be generated, no assessment or conclusions on the compliance can currently be made. Should you decide to pursue the strategy presented in your comments, ECHA will assess the compliance in the follow-up to the dossier evaluation.

2. 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 included a data waiver in your dossier with a justification referring to Annex X, Section 8.7., Column 2, third indent.

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 of no systemic toxicity. Although there is no evidence of toxicity in the available study (28-day study), the highest dose used in this study was not the limit dose (1000 mg/kg bw/day) and you have not provided any toxicokinetic data to support your claim of no systemic absorption. Furthermore, the uses of the Substance 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 second species, depending on the species tested in the first PNDT study (request B.2 in this decision).

The study shall be performed with oral[9] administration of the Substance.

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

In the comments, you present a strategy to fulfil this information requirement relying on the generation of additional supporting information on the Substance and on the analogue substance Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane (HDDGE, EC 618-939-5), 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 the OECD 414 study in a first species yet to be conducted on the Substance as requested in Appendix B, Section 2, and the available data from an OECD 414 study on HDDGE, you will decide on whether the PNDT study in a second species should be performed on BDDGE, or HDDGE and read across to BDDGE.

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 the compliance in the follow-up to the dossier evaluation.

Appendix D: 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[10].

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[11].

[10] https://echa.europa.eu/practical-guides
[11] https://echa.europa.eu/manuals

Appendix E: 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 F: Procedure

The information requirement Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. Your testing proposal will be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided in your registration dossier. This is due to the fact that the results from the 90-day study is needed for the assessment of the testing proposal design of the EOGRTS.

Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision, as an EOGRTS may cover the same parameters.

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

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

The compliance check was initiated on 29/08/2019.

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

ECHA took into account your comments and amended the deadline for all requests except for request B.1; ECHA did not amend the requests as such.

> In your comments on the draft decision, you requested to delete the 12 months deadline for the information requested under B.1, and to align the timeline of 30 months for the other information requests in this decision with the timeline for the decision on Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane (EC 618-939-5, HDDGE) of 36 months. You justified your request by stating that the OECD 408 study (request B.1) is not required due to an improved read-across justification, and by the common approach for the two substances 1,4-bis(2,3-epoxypropoxy)butane and HDDGE as outlined in your comments.
>
> As explained in Appendix B.1, ECHA agrees with your reasoning regarding the request B.1, but did not amend the request (for the reasons see Appendix B, section 1 below); you are responsible to provide the information in the dossier in an update of the registration, by the deadline set in this decision.
>
> Independently of the above, ECHA agrees to extend the deadline for the other requests by 6 months, i.e. from 30 to 36 months, to align with the deadline set in the decision on HDDGE.

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.

You provided comments only on the draft decision. Your 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 G: List of references - ECHA Guidance[12] 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)[13]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[13]

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.

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

OECD Guidance documents[14]
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.

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

Appendix H: 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.