~~Confidential~~

Helsinki, 10 October 2023

Addressee(s)
Registrant(s) of JS_701-197-2 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
19/07/2022

Registered substance subject to this decision ("the Substance")
Substance name: Reaction products of 2-(chloromethyl)oxirane and glycerol
EC number/List number: 701-197-2

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***15 January 2026***.

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

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

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

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

3. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203).

The reasons for the request(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 request(s)
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

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

Appendix 1: Reasons for the request(s)

Contents

Reasons common to several requests

0.1. Weight of evidence adaptation rejected

1 You have adapted the following standard information requirements by using Annex XI, Section 1.2. (weight of evidence):

- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.);
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.).

2 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

3 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

4 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude on the corresponding information requirement.

5 Your weight of evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually.

6 The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in request(s) 1 and 2 below.

0.1.1. Lack of robust study summaries for some sources of information

7 Annex XI, Section 1.2. requires that whenever weight of evidence is used adequate and reliable documentation of the applied method must be provided. Such documentation must include a robust study summary for each source of information used in the adaptations.

8 A robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

9 In addition, for weight of evidence adaptations, the robust study summary must clearly indicate which key parameters of the study normally required for the information requirement are investigated in the study.

10 For the information requirement on repeated dose toxicity, you have provided information from a peer-reviewed handbook (1981) and in the endpoint study record explain that "As this information comes from a peer-reviewed handbook, not all the data concerning i.e. methods and guidelines followed are specified."

11 For the information requirement on reproductive toxicity, you have provided information in the form of:

- OECD QSAR Toolbox prediction reports (Toolbox prediction report) which describe suitable candidates for analogue substances, but do not contain information in a form of robust study summaries; and

- statements describing reproductive toxicity properties of various substances (Request 2, Section 2.1.1, sources of information (vi) and (x), but have not provided this information in the form of robust study summaries.

12 The above described sources of information do not contain detailed summaries of the objectives, methods, results and conclusions of the respective studies the information refers to. Therefore, it is not possible to make an independent assessment of the relevance of the study including whether the key parameters of the study normally required for the information requirements are investigated in the respective studies.

13 Consequently, you have failed to provide robust study summaries as required by Annex XI, Section 1.2 for these sources of information. Therefore, these sources of information, i.e. the information from the peer-reviewed handbook (1981), as a form of Toolbox prediction reports as described below under the relevant information requirements, and statements noted under Request 2, Section 2.1.1, sources of information (vi) and (x) cannot be taken into account in the assessment of your weight of evidence adaptation because it is not possible to independently confirm the relevance and reliability of the information provided.

0.1.2. Reliability of information provided with analogue substances

14 You intend to predict the toxicological properties of the Substance for the above listed information requirements from the information obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation. For this information to be considered reliable, it would have to meet the requirements for Grouping of substances and read-across approach.

15 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.

16 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).

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

18 For toxicological properties, you predict the properties of the Substance from information obtained from the following substances:

- Polyglycidyl ether of substituted glycerin (EPON 562) (source substance 1);
- Glycidol CAS 556-52-5 (source substance 2);
- Allyl glycidyl ether CAS 106-92-3 (source substance 3);
- Isopropyl glycidyl ether CAS 4016-14-2 (source substance 4);
- Phenyl glycidyl ether CAS 122-60-1; EC 204-557-2 (source substance 5);
- n-Butyl glycidyl ether CAS 2426-08-6 (source substance 6)
- Diglycidyl ether, CAS 2238-07-5 (source substance 7)
- Epichlorohydrin, EC 203-439-8 (source substance 8)
- 7-oxabicyclo-hept-3-ylmethyl 7-oxabicyclo-heptane-3-carboxylate, CAS 2386-87-0 (source substance 9)
- Ethylene oxide, CAS 75-21-8 (source substance 10).

19 You provide the following reasoning for the prediction of toxicological properties: You consider that the substances have closely related chemical structures, possess similar physico-chemical properties, have very similar endpoint specific mechanisms/modes of

action, structural alerts, functional groups etc. based on OECD QSAR Toolbox, and have similarities in toxicological behaviour.

20 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 substances.

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

22 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.).

23 Supporting information must include supporting information/bridging studies to compare properties of the source substances.

24 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar source substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the source substance(s) is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration with the Substance and the source substance(s).

25 To support the predictions for the repeated dose toxicity and reproductive toxicity properties, you have provided profiling results from the OECD QSAR Toolbox v.3.0. indicating that the substances have similar endpoint specific mechanisms/modes of action. In addition, for the Substance and for the source substances you have provided information for acute toxicity, irritation/corrosion, sensitisation and for genetic toxicity.

26 We have evaluated the information and identified the following issues:

27 First, the information from the QSAR predictions may indicate that the structural differences within the category members do not influence the reactivity of the substances. However, due to the complexity of the systemic interactions as well as the large number of targets/mechanisms associated with repeated dose and reproductive (including developmental) toxicity, the information from the computational tools need to be supported by further, relevant, experimental data.

28 Second, the information on the acute toxicity, local toxicity (irritation/corrosion and sensitisation) and genetic toxicity properties do not inform on the repeated dose toxicity or reproductive toxicity properties, and therefore, the comparison of such data between the Substance and source substances is not considered as relevant to support your read-across hypothesis.

29 Third, you have not provided any data on the Substance for repeated dose toxicity and reproductive toxicity to allow comparison with the source substance(s).

30 Based on above, you have not provided adequate supporting information to establish that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

31 As a conclusion, due to the issues identified above in the read-across approach, the information from the analogue substances do not reliably contribute to a weight of evidence intended to identify the properties of the Substance.

0.1.3. Reliability of information provided via dermal and inhalation routes

32 To allow conclusive determination of a particular toxicological property for systemic toxicity, the choice of the route of administration must ensure that systemic availability (internal dose) of the substances is maximised.

33 Annex VIII, 8.6.1, describes the selection of appropriate route for the repeated dose toxicity studies and the ECHA Guidance on IRs and CSA R 7.a (R.7.5.4.3.2) stipulates, "*Concerning repeated dose toxicity testing, the oral route is the default one because it is assumed to maximise systemic availability (internal dose) of most substances*."

34 Under Annex VIII, Section 8.7.1, the route of administration for the Screening for reproductive/developmental toxicity study should be oral if the substance is a solid or a liquid, and inhalation if the substance is a gas. Deviations may be justified, for example through evidence of equivalent or higher systemic exposure via another route of human exposure or route-specific toxicity.

35 For the repeated dose and reproductive toxicity endpoints, you have provided information via inhalation and dermal routes of exposure for the source substances which are not gases.

36 The information is not provided via the default oral route that is assumed to maximise the systemic availability of the substances. You have not provided any information such as toxicokinetic information to demonstrate that the substances administered via inhalation and dermal routes are absorbed, distributed in the body, and become systemicly available in the same way as would be expected after administration via the default oral route, and will not underestimate the hazard.

37 Therefore, you have not demonstrated that the systemic availability of the tested substances would be maximised via the non-default dermal and inhalation routes and the information from studies conducted via dermal or inhalation routes do not reliably contribute to a weight of evidence intended to identify the systemic toxicity properties of the Substance.

38 In your comments to the draft decision you "*agree that the applied read-across approach has some shortcomings*", however, you did not comment on ECHA's assessment, and you did not provide any new information. Instead, you refer to "*the ongoing assessment of regulatory needs (ARN) for the group of glycidyl ethers and esters*". You indicate that "*ECHA grouped together structurally similar substances based on the presence of the glycidyl moiety*" and "*the registered substance is considered within the sub-group of "Glycidyl ethers – Aliphatic polyglycidyl ethers", a group comprising a total of 11 substances of which 9 substances have full REACH registrations*". Based on the information, provided in the ARN report, you point out that "*a series of repeated dose-type toxicity studies, especially studies on reproductive toxicity will be or are currently being conducted on structurally related substances belonging to the group of glycidyl ethers and esters, and more specifically to the sub-group of "Glycidyl ethers – Aliphatic polyglycidyl ethers*".

39 You conclude that "*It is considered most reasonable to assess the hazard of this group in a read-across approach to avoid unnecessary animal testing*" and you ask ECHA "*to first evaluate the results obtained in these studies to clarify whether these structurally related substances share a common reproductive mode of action"* and "*The decision of a potential need for further substance-specific data*" should be based on the obtained results.

40 In addition you state that the Substance "*has already been self-classified as reproductive toxicant [..] based on the read-across information" and "this potential hazard is already included in the risk assessment and communicated via safety data sheets".*

41 Firstly, ECHA points out that objectives of the compliance check process and the assessment of regulatory needs (ARN) are different. The purpose of the ARN for a group of substances is to help authorities conclude on the most appropriate way to address the identified

concerns, if any, for a group of substances or a single substance. For more information on the 'Working with Groups' please visit: https://echa.europa.eu/working-with-groups.

42 The objective of the compliance check process is to identify potential data-gaps and require the submission of the information needed to fill those potential data-gaps. For the reasons explained in this decision, your dossier is found incompliant for the information requirements, *inter alia*, of Annex VIII, Section 8.6.1 and Annex VIII, Section 8.7.1. Therefore, studies to address these information requirements are requested.

Further, in your comments to the draft decision you state that "*The decision of a potential need for further substance-specific data should be based on"* the results of the studies to be performed with structurally related substances belonging to the sub-group of "Glycidyl ethers – Aliphatic polyglycidyl ethers", in order to identify "[..] whether *the common glycidyl moiety indeed causes reproductive toxicity irrespective of the backbones and further chemical structures contained, or whether individual evaluations of all substances is warranted*."

As already explained above, the grouping of substances for the purpose of ARN is to speed up the identification of chemicals that need regulatory action, and authorities may decide to address groups of structurally related substances rather than single substances. The work is different from grouping and read-across as defined in Section 1.5 of Annex XI to REACH. Therefore, if you consider that the reproductive and developmental toxicity properties of your Substance can be predicted from information on structurally similar substances, it is at your own discretion to adapt the information requirement in accordance with the general rule for adaptation, defined in Section 1.5 (read across) of Annex XI to REACH

Last, the adaptation according to section 1.2. (WoE) of Annex XI of REACH, currently included in your dossier is rejected, for the reasons explained in this decision. As a consequence, any conclusion drawn on its basis for the purposes of hazard identification and risk assessment, including classification and labelling is not reliable.

Reasons related to the information under Annex VIII of REACH

1. Short-term repeated dose toxicity (28 days)

43 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1.

1.1. Information provided

44 You have adapted this information requirement by using Annex VIII, Section 8.6.1., Column 2.

45 You have provided the following justification: "*a short-term toxicity study does not need to be conducted because a reliable sub-chronic (90 days) or chronic toxicity study is available, conducted with an appropriate species, dosage, solvent and route of administration*".

46 You have provided the following multiple sources of information which ECHA understands you meant as a weight of evidence adaptation under the Annex XI, Section 1.2.:

(i) an oral sub-chronic repeated dose toxicity study (1958) with the source substance 1;

(ii) an oral chronic repeated dose toxicity study (reference to peer-reviewed handbook, 1981) with the source substance 1;

(iii) an inhalation short-term repeated dose toxicity study (1958) conducted with the source substance 1;

(iv) an inhalation short-term repeated dose toxicity study (reference to peer-reviewed handbook, 1981) conducted with the source substance 1;

(v) an inhalation short-term repeated dose toxicity study (1956) conducted with source substances 2, 3, 4, and 5;

(vi) an inhalation sub-chronic repeated dose toxicity study (1977) conducted in rats with the source substance 5;

(vii) an inhalation sub-chronic repeated dose toxicity study (1977) conducted in dogs with the source substance 5;

(viii) a dermal short-term repeated dose toxicity study, Draize method (1958) conducted with the source substance 1;

(ix) a dermal repeated dose toxicity study, Draize method (1956) conducted with the source substances 2, 3, 4, 5, 6 and 7;

(x) a dermal short-term repeated dose toxicity study (reference to peer-reviewed handbook, 1981) conducted with the source substance 1 (20 applications);

(xi) a dermal short-term repeated dose toxicity study (reference to peer-reviewed handbook, 1981) conducted with the source substance 1 (5 applications);

(xii) a dermal short-term repeated dose toxicity study (reference to peer-reviewed handbook, 1981) conducted with the source substance 1 (20 applications);

(xiii) an intramulcular repeated dose toxicity study (reference to peer-reviewed handbook, 1981) conducted in rats with the source substance 1;

(xiv) an intramulcular repeated dose toxicity study (reference to peer-reviewed handbook, 1981) conducted in dogs with the source substance 1;

(xv) an intravenous repeated dose toxicity study (reference to peer-reviewed handbook, 1981) conducted in dogs with the source substance 1;

(xvi) an intravenous repeated dose toxicity study (reference to peer-reviewed handbook, 1981) conducted in rabbits with the source substance 1.

1.2. Assessment of the information provided

1.2.1. Adaptation under Annex VIII, Section 8.6.1., Column 2 in combination with Annex XI, Section 1.2. is rejected

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

48 You have provided multiple sources of information (i-xvi) for the sub-chronic (90 days) study, and therefore, ECHA has evaluated the provided information under Annex XI, Section 1.2. (weight of evidence).

49 As explained under Section 0.1 on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information.

50 As explained in Section 0.1.1., the sources of information (ii), (iv), and (x-xvi) are from a peer-reviewed handbook (1981) and cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration as no robust study summaries were provided.

51 In addition to the deficiencies identified in Section 0.1, ECHA identified endpoint specific issue(s) addressed below.

52 Relevant information that can be used to support weight of evidence adaptation for a reliable sub-chronic (90 days) study includes similar information that is produced by the OECD TG 408. The OECD TG 408 requires the study to investigate the following key elements:

(1) in life observations;
(2) blood chemistry;
(3) organ and tissue toxicity.

1.2.1.1. In life observations

53 In-life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

54 The sources of information (i), (iii) and (v-ix) provide relevant information on in life observations.

55 However, for the reasons explained in the section 0.1.2. and 0.1.3. of the Reasons common to several requests above, you have not established that the information on the analogue substance(s) for sources of information (i), (iii) and (v-ix) and the information from the studies conducted via dermal or inhalation routes for sources of information (iii) and (v-ix) can reliably contribute to your weight of evidence adaptation.

1.2.1.2. Blood chemistry

56 Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary)

57 The sources of information (i), (iii) and (viii-ix) do not provide relevant information on blood chemistry.

58 The sources of information (v-vii) provide relevant information on blood chemistry.

59 However, for the reasons explained in the section 0.1.2. and 0.1.3. of the Reasons common to several requests above, you have not established that the information on the analogue substances and the information from the studies conducted via inhalation routes for sources of information (v-vii) can reliably contribute to your weight of evidence adaptation.

1.2.1.3. Organ and tissue toxicity

60 Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

61 The sources of information (viii-ix) do not provide relevant information on the organ and tissue toxicity.

62 The sources of information (i), (iii) and (v-vii) provide relevant information on the organ toxicity.

63 However, for the reasons explained in the section 0.1.2. and 0.1.3. of the Reasons common to several requests above, you have not established that the information on the analogue substance for sources of information (i), (iii) and (v-vii) and the information from the studies conducted via inhalation route for sources of information (iii) and (v-vii) can reliably contribute to your weight of evidence adaptation.

64 In summary, the sources of information (v-vii) provide relevant information on all key elements of the repeated dose toxicity study, while sources of information (i), (iii) and (viii-ix) provide limited information on some of the key elements only (in life observations and/or organ toxicity). However, all these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the 90-day repeated dose toxicity.

1.3. Conclusion on the information provided

65 Based on the above, you have not provided a reliable sub-chronic (90 days) or chronic toxicity study, and therefore, the adaptation under Annex VIII, Section 8.6.1, column 2 is is rejected.

66 Therefore, the information requirement is not fulfilled.

1.4. Specification of the study design

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

68 The study design is addressed in request 2.

69 In your comments to the draft decision you "*agree that the applied read-across approach has some shortcomings*". However, you did not provide any new information but indicate that "*ECHA added the registered substance to the group of "Glycidyl ethers – Aliphatic polyglycidyl ethers*" and you refer to "*the ongoing assessment of regulatory needs (ARN) for the group of glycidyl ethers and esters".* You indicate that "*this group contains structural analogue substances, for which new robust guideline studies are currently being conducted"* and *"it is considered most reasonable to assess the hazard of this group in a read-across approach to avoid unnecessary animal testing"*.

70 For the reasons, explained in section 0.1. above, the information requirement is not fulfilled.

2. Screening study for reproductive/developmental toxicity

71 A screening study 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.

2.1. Information provided

72 Under the Toxicity to reproduction, IUCLID Section 7.8.1. you have provided the following multiple sources of information which ECHA understands you meant as a weight of evidence adaptation under the Annex XI, Section 1.2.:

(i) an oral one-generation reproductive toxicity study (1989) conducted with the source substance 8;

(ii) an inhalation two-generation reproductive toxicity study (1982) conducted with the source substance 5; and

(iii) Toolbox prediction report for reproductive toxicity of the source substance 8.

(iv) Toolbox prediction report for reproductive toxicity of the source substances 3 and 10.

(v) Toolbox prediction report for reproductive toxicity of the source substances 2 and 5.

(vi) The statement: "*No adverse effects on the ovaries and testes (dermal, 13-w, rats, HPV, 2002)*" with reference to alkyl glycidyl ether (CAS 68609-97-2).

73 You justify the adaptation as follows: "*Experimental data revealed that the related substance Epichlorohydrin induces adverse effects on male fertility at 12.5 mg/kg/day. Related substances that contain glycidyloxy moieties in their structures produced damage of male fertility and testicular atrophy. The pattern of toxicity was similar in numerous animal studies. Based on the significant body of evidence, reproductive toxicity of the target substance GE-100 can not be ruled out*."

74 In addition, under the developmental toxicity you have provided information for the developmental toxicity/teratogenicity (IUCLID Section 7.8.2) which is not an information requirement at Annex VIII. Therefore, ECHA understands that you have provided the following information in an attempt to adapt the information requirement of Annex VIII, 8.7.1 according to Annex VIII, Section 8.7., Column 2 in conjunction with Annex XI, Section 1.2.:

(vii) a pre-natal developmental toxicity study (1982) conducted in rats and mice with the source substance 2;

(viii) a pre-natal developmental toxicity study (1982) conducted in rats and mice with the source substance 8; and

(ix) Toolbox prediction report for pre-natal developmental toxicity of the source substances 2, 8 and 9;

(x) The statement: "*No influence on embryonic or pup development was observed in the 13- week repeated dose toxicity and fertility study conducted with triglycidyl isocyanurate (HPV, No. 201 -15759).*"

75 You justify the adaptation as follows: "*No evidence of developmental toxicity was found in the numerous studies available for structurally similar chemicals. Therefore, in analogy to other epoxides, no developmental toxicity can be assigned for the target substance*."

2.2. Assessment of the information provided

2.2.1. Adaptation under Annex XI, Section 1.2. is rejected

76 As explained in Section 0.1., there are common deficiencies in your adaptation based on weight of evidence under Annex XI, Section 1.2. In addition, ECHA identified endpoint specific issue(s) addressed below.

77 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.7.1. includes similar information that is produced by the OECD TG 421. OECD TG 421 requires the study to investigate the following key elements:

(1) sexual function and fertility;
(2) toxicity to offspring;
(3) systemic toxicity.

78 As explained under Section 0.1 on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information.

79 As explained in Section 0.1.1., the sources of information (iii-v: Toolbox prediction reports), and the statement (vi) cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration, as no robust study summaries were provided.

80 The sources of information (i) and (ii) may provide relevant information on sexual function and fertility, offspring development and systemic toxicity.

81 However, for the reasons explained in the section 0.1.2. and 0.1.3. of the Reasons common to several requests above, you have not established that the information on the analogue substance for sources of information (i) and (ii) and the information from the studies conducted via inhalation routes for source of information (ii) can reliably contribute to your weight of evidence adaptation.

82 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for the screening reproductive/developmental toxicity study.

83 Based on the above, your weight of evidence adaptation for the screening reproductive/developmental toxicity study is rejected.

2.2.2. Adaptation under Column 2 of Annex VIII, section 8.7. in conjunction with Annex XI, Section 1.2 fails

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

85 The sources of information (vii) to (ix) are described as a pre-natal developmental toxicity studies and the statement (x) refers to developmental toxicity. As you have provided information with multiple source substances and species, ECHA has evaluated the information under the Annex XI, Section 1.2. (weight of evidence).

86 As explained in Section 0.1., there are common deficiencies in your adaptation based on weight of evidence under Annex XI, Section 1.2. In addition, ECHA identified endpoint specific issue(s) addressed below.

87 Relevant information that can be used to support weight of evidence adaptation for pre-natal developmental toxicity includes similar information that is produced by the OECD TG 414 on one species. The following aspects are covered:

(1) prenatal developmental toxicity,

(2) maternal toxicity, and

(3) maintenance of pregnancy.

88 As explained in Section 0.1.1, the sources of information (ix; Toolbox prediction report), and the statement (x) cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration, as no robust study summaries were provided.

89 The sources of information (vii-viii) may provide relevant information on prenatal developmental toxicity, maternal toxicity, and maintenance of pregnancy.

90 However, as explained in Section 0.1.2., due to the issues identified in the read-across approach, the information from the analogue substance for sources of information (vii-viii) does not reliably contribute to a weight of evidence intended to identify the properties of the Substance.

91 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the pre-natal developmental toxicity.

92 Based on the above, your weight of evidence adaptation for the pre-natal developmental toxicity is rejected.

93 Therefore, as the dossier does not contain a reliable pre-natal developmental toxicity study, the adaptation under Column 2 of Annex VIII, section 8.7. in conjunction with Annex XI, Section 1.2 is rejected.

2.3. Conclusion on the information provided

94 As a conclusion, your adaptations are rejected, and the information requirement is not fulfilled.

95 In your comments to the draft decision you "*agree that the applied read-across approach has some shortcomings*". However, you did not provide any new information but indicate that "*ECHA added the registered substance to the group of "Glycidyl ethers – Aliphatic polyglycidyl ethers*" and you refer to "*the ongoing assessment of regulatory needs (ARN) for the group of glycidyl ethers and esters".* You indicate that "*this group contains structural analogue substances, for which new robust guideline studies are currently being conducted"* and *"it is considered most reasonable to assess the hazard of this group in a read-across approach to avoid unnecessary animal testing"*.

96 For the reasons, explained in section 0.1. above, the information requirement is not fulfilled.

2.4. Specification of the study design

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

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

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

3. Short-term toxicity testing on fish

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

3.1. Information provided

101 You have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided a prediction from Danish QSAR Database.

102 In addition, you have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on data from structural analogue substances identified using the OECD QSAR toolbox and selected from Aquatic OASIS, ECHA CHEM and ECOTOX or Aquatic ECETOC database(s).

3.2. Assessment of the information provided

3.2.1. QSAR adaptation rejected

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

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

104 You reported a Danish QSAR database prediction on the Substance in IUCLID Section 6.1.1.

3.2.1.1. With regard to these conditions, we have identified the following issue(s):Inadequate documentation of the prediction (QPRF)

105 ECHA Guidance R.6.1.6.3. states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the relationship between the modelled substance and the defined applicability domain;
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

106 You provided the following information about the prediction: a prediction report from QSAR toolbox; information on Leadscope Enterprise model; and information on SciMatics SciQSAR model.

107 The information you provided about the prediction lacks the following elements: the applicability domain assessment provided in the report of the software does not include an explanation on how the specific target substance fits the applicability domain. There is no information on the identity of close analogues and/or considerations on how predicted and experimental data for analogues support the prediction.

108 In absence of such information, ECHA cannot establish that the conditions of the adaptation are met.

109 Based on the above, your QSAR adaptation under Annex XI, Section 1.3. is rejected.

3.2.2. Read-across adaptation rejected

110 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.

111 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).

112 You provide the read-across justification documents *"QSAR Toolbox prediction for single chemical"* and *"QSAR Toolbox prediction for multicomponent substances"* as attachments to the endpoint study record in IUCLID Section 6.1.1.

113 You justify the grouping of the substances as:

- Substances have the same epoxy moiety or are percursors of the target substance;
- Substances belong to the same glycidyls category;
- Substances have similar profiling result regarding the ability to bind to proteins.

114 You define the the structural basis for the grouping as "*epoxides represent hazard to the aquatic environment if their molecular weight is lower than 1000 g/mol and logPow < 5 (EPA, 2010). Common properties of epoxides are high reactivity and cytotoxicity*", "*the target substances and the read-across substances belong to the category of glycidyls (HPV, Epoxy Resin Systems Task Group (ERSTG), 2001)*".

115 ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

116 You predict the properties of the Substance from information obtained from the following source substance(s):

117 For "QSAR Toolbox prediction for single chemical"

- C=CCOCC1CO1 (allyl glycidyl ether)
- C(C1CO1)Oc1ccccc1 (phenylglycidyl ether)
- C(C1CO1)Oc1ccccc1 (2-(phenoxymethyl)oxirane)

118 For "QSAR Toolbox prediction for multicomponent substances"

- OCC1CO1 (glycidol)
- C1C(C2CO2)O1 (1,2:3,4-diepoxybutane)
- C(CCCOCC1CO1)OCC1CO1 (1,4-bis(2,3-epoxypropoxy)butane)

- C1CO1 (ethylene oxide)
- ClCC1CO1 (epichlorohydrin)
- ClCC1CO1 (2-(chloromethyl)oxirane)
- C(CCCCOCC1CO1)OCC1CO1 (1,6-bis(2,3-epoxypropoxy)hexane)
- C(CCCC1CO1)C1CO1 (1,2,7,8-diepoxyoctane)

119 You provide the following reasoning for the prediction of ecotoxicological properties: "The aquatic toxicity potential of epoxides with low molecular weight would represent worst case for aquatic toxicity potential of epoxides with higher molecular weights. According to EPA (2010), "there is greater concern for primary epoxides, than for epoxides with substitutions on both of the epoxy carbons".

120 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 based on a worst-case approach.

121 We have identified the following issue(s) with the prediction of ecotoxicological properties:

3.2.2.1. Inadequate read-across hypothesis

122 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 include an explanation why the properties of the Substance may be predicted from other substances in the group, i.e. a read-across hypothesis. This hypothesis should be based on recognition of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.). It should explain why the differences in the chemical structures should not influence the ecotoxicological properties or should do so in a regular pattern, taking into account that variations in chemical structure can affect both toxicokinetics (uptake and bioavailability) and toxicodynamics (e.g. interactions with receptors and enzymes) of substances (Guidance on IRs and CSA, Section R.6.2.1.3).

123 Your read-across hypothesis is only based on similar profiling and the structural similarity between the source substance(s) and the Substance i.e. presence of epoxide moiety, which you consider a sufficient basis for predicting the properties of the Substance. You support your assumption of the worst case in the following way "epoxides represent hazard to the aquatic environment if their molecular weight is lower than 1000 g/mol and logPow < 5".

124 The Substance is a UVCB. You report that the category members are mono-constituent substances of variable chemical structure.

125 You consider primary epoxides more toxic and that the epoxide moieties of the Substance are covered in the category members.

126 However, your hypothesis does not explain why the structural differences between the substances do not influence the ecotoxicological properties or do so in a regular pattern.

127 While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar ecotoxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a ecotoxicological property, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances, and thus why the properties of the Substance may be predicted from information on the source substance(s).

3.2.2.2. Missing supporting information to substantiate worst-case consideration

128 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.).

129 Supporting information must include information to compare properties of the category members, including the Substance.

130 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. In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and 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 bridging studies of comparable design and duration for the source substance(s).

131 You provide QSAR toolbox prediction for "single chemicals" and "multicomponent substances", in the registration dossier. In the respective prediction documents you indicate that the calculation of the effect value is based on "the average value from the [..] nearest neighbours". You only report the effect values for each neighbour i.e., category member, without information on the experimental method used. Therefore, you do not provide enough information to allow an independent assessment of the quality of the predictions for the category members.

132 Additionally, your dossier does not contain reliable information on the Substance, as explained under section 2.2.1.1. above. Therefore, your have not provided information that would allow to compare the properties of the Substance and the source substance(s) for a conservative prediction of the properties of the Substance.

133 In the absence of such information, you have not established that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

134 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the category members. On this basis, your read-across approach under Annex XI, Section 1.5. is rejected.

135 Therefore, the information requirement is not fulfilled.

136 In the comments on the draft decision, you agreed to perform the requested study. However, you expect that fish is not the most sensitive species and that in general the Substance is not expected to be toxic to aquatic organisms considering the studies on algae and Daphnia. Therefore you propose to perform first a limit test using the threshold concentration of 100 mg/L and only if mortality occurs, perform the full study.

137 This approach follows the OECD TG 203 and can fulfil the information requirement. However, as the study is not yet submitted in the registration dossier, compliance of the information cannot be evaluated. You remain responsible for complying with this decision by the set deadline.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).
All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

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

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

The compliance check was initiated on 01 February 2022.

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

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

ECHA took into account your comments and did not amend the requests.

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

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

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

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

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

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

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

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

1.2. Test material

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

(1) Selection of the Test material(s)

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

- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with

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

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 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).