ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 13 December 2019

Addressees
Registrant(s) who have opted out from the joint submission JS_112-15-2 listed in Appendix G of this decision

Date of submission subject of this decision
14 February 2018

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

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 2-(2-ethoxyethoxy)ethyl acetate
EC number: 203-940-1
CAS number: 112-15-2

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline provided and with the Substance:

A. Requirements subject to Annex VI of REACH

1. **Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for long-term aquatic hazard or provide a justification for not classifying;**

B. Requirements subject to Annex VII of REACH

1. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method EU B.13/14. / OECD TG 471) ;**

C. Requirements subject to Annex VIII of REACH

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

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained ;**

3. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route;**

D. Requirements subject to Annex IX of REACH[1]

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test**

[1] Testing required under this Annex can only be started or performed after the decision has been adopted according to Article 51.

method OECD TG 414) in a first species (rat or rabbit), oral route;

2. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210).**

Conditions to comply with the requested information

You are bound by the requests for information corresponding to the REACH Annexes applicable to your registered tonnage of the Substance at the time of evaluation. You have registered the Substance at 100-1000 tonnes per annum, and therefore, you have to comply with the requirements of Annexes VI-IX of REACH.

The Appendix on General Considerations addresses the arguments applicable throughout Appendices A to D of the present decision (such as the conditions for applying adaptations based on Weight of evidence, Qualitative or Quantitative structure-activity relationship ((Q)SAR) or grouping and read-across).

Appendices A to D state the reasons for the requests for information to fulfil the requirements set out respectively in Annexes VI-IX to REACH.

Deadline to submit the requested information

You are required to submit the information requested in this decision in an updated registration dossier by ***20 September 2021***.
You shall also update the chemical safety report, where relevant, including any changes to classification and labelling based on the newly generated information. The timeline has been set to allow for sequential testing.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[2] under the authority of Christel Schillinger-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.

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Appendix on General considerations

Your registration dossier contains adaptation arguments for the information requirements addressed in this decision (requests B.1 – D.2) either in the form of using existing information according to Annex XI, Section 1.1.2., a weight-of-evidence approach according to Annex XI, Section 1.2., predictions generated with QSAR models under Annex XI, Section 1.3. and/or grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. A list of references to ECHA Guidance documents containing further information on these adaptations are listed in Appendix F of this decision.

For each relevant endpoint, ECHA has assessed your adaptation arguments in line with the conditions specified in Annex XI of the REACH Regulation:

(i) For the use of existing data on human health and environmental properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3), according to Annex XI, Section 1.1.2., the following cumulative conditions need to be necessarily met:

- Adequacy for the purpose of classification and labelling and/or risk assessment;
- Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
- Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
- Adequate and reliable documentation of the study is provided.

(ii) For the use of adaptations using Weight of Evidence (WoE) according to Annex XI, Section 1.2., it should be demonstrated that there is sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property with respect to the information requirement in question while the information from each single source alone is regarded insufficient to support this notion.

A weight of evidence adaptation shall include an assessment of the relative values/weights of different pieces of the available information which is defined by e.g. the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory endpoint. Subsequently, the lines of evidence should be integrated considering their relative values or weights in order to draw a conclusion (ECHA Guidance R.4.4). Adequate and reliable documentation shall be provided to describe your WoE approach, the assessment of relative weights of individual piece of information and the subsequent conclusions drawn.

Whenever sources of information derived from analogue substances are used as part of a WoE, the characterisation of the analogue substance(s) identified needs to be as detailed as possible and a reasoning needs to be provided to establish why information from analogue substance(s) can reliably be read-across.

(iii) For the use of QSAR models under Annex XI, Section 1.3., the following cumulative conditions shall be necessarily met: results are derived from a (Q)SAR model whose scientific validity has been established; the substance falls within the applicability domain of the model; results are adequate for the purpose of classification and labelling and/or risk assessment; adequate and reliable documentation of the applied method is provided.

(iv) For the use of read-across approach according to Annex XI, Section 1.5., two conditions

shall be necessarily fulfilled. 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. Unambiguous substance identity for both the source substance and the target substance is therefore a prerequisite for a read-across assessment. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data on reference substance(s) within the group (read-across approach).

For this purpose, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances (ECHA Guidance R.6.2). This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

Appendix A: Reasons for the requests to comply with Annex VI of REACH

1. Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for long-term aquatic hazard or provide a justification for not classifying

In accordance with Article 10(a)(iv) of REACH, a technical dossier shall contain information on classification and labelling of the substance as specified in Annex VI, Section 4 of REACH in conjunction with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation).

Annex VI, Section 4.1 of REACH states that the hazard classification of a substance shall result from the application of Titles I and II of the CLP Regulation. In addition, for each entry, the scientifically justified reasons why no classification is given for a hazard class or differentiation of a hazard class should be provided. According to Article 5(1) of Title I of the CLP Regulation, a substance shall be classified on the basis of available information.

Furthermore, the technical dossier must include the resulting hazard label for the substance in line with Title III of the CLP Regulation (Annex VI, section 4.2 of the REACH Regulation).

According to the CLP Regulation, Annex I, Section 4.1, classification of a substance as hazardous to the aquatic environment recognises that the intrinsic hazard to aquatic organisms is represented by both the acute and long-term hazard of a substance. For the long-term hazard (Table 4.1.0 (b)), separate hazard categories are defined representing a gradation in the level of hazard identified for (i) Non-rapidly degradable substances for which there are adequate chronic toxicity data available, (ii) Rapidly degradable substances for which there are adequate chronic toxicity data available, and (iii) Substances for which adequate chronic toxicity data are not available. The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algae/aquatic plants) shall normally be used to define the appropriate hazard category(ies).

You have reported that the substance is readily biodegradable based on a weight of evidence approach; one line of evidence indicating degradation of 101% in 30 day study ([redacted] 2012). The results indicate a rapid degradation of the registered substance. According to Table 4.1.0 (b)(ii) of the CLP Regulation, Annex I, Section 4.1, for a rapidly degradable substance for which there are adequate chronic toxicity data available, Category Chronic 3 is indicated when Chronic NOEC or EC50 for fish, crustacean or algae/aquatic plants is ≤1 mg/L.

You have not classified the substance, and provided the following justification: "*conclusive but not sufficient for classification.*" You further state that "*Also the substance 2-(2-ethoxyethoxy) ethyl acetate is readily biodegradable in nature and BCF value is <500. Thus considering the criteria of CLP classification, 2-(2-ethoxyethoxy) ethyl acetate is not toxic to aquatic environment.*"

ECHA notes that you have submitted a study on long-term toxicity testing on invertebrates (Devillers et al. 2003, Chemosphere 50:330-376) and reported an EC10 of 0.125 mg/L (*C. dubia*, 7-d including 3 broods, reproduction). This study indicates that toxicity may occur in concentrations lower than 1 mg/L, indicating thus that classification of the substance should be considered also for a rapidly degradable substance. Your justification for not classifying the substance for long-term aquatic hazard does not consider this long-term toxicity study on *C.dubia*.

All the information submitted in your IUCLID dossier and additionally the information requested in this decision (request D.2) should be considered for classification of the registered substance.

Appendix B: Reasons for the requests to comply with Annex VII of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to the REACH Regulation.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An *In vitro* gene mutation study in bacteria is a standard information requirement under Annex VII to the REACH Regulation.

You have adapted the standard information under Annex XI, Section 1.2., Weight of evidence, by providing two endpoint study records and indicated the adequacy of studies as "weight of evidence". The conditions for adapting the standard information under this general rule are further explained in the Appendix on general considerations above.

In your registration dossier you have provided the following information:

(i) You have indicated "(Q)SAR" in the administrative section of one endpoint study record in the technical dossier for this endpoint. You further provided an automated report generated with the OECD QSAR Toolbox.

(ii) *In vitro* gene mutation study in bacteria with the Substance (according to: 84/449/EWG B.14, GLP not specified, SDS report 2005). Negative in *S. typhimurium* strains: TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation. You assigned a reliability score of 4 "not assignable" with a rationale "Data from SDS Dossier report".

ECHA's assessment of the provided information:

Regarding the information under point (i), the QSAR toolbox report states that it is used to predict gene mutation for the Substance based on read-across from analogue substances. Therefore, as explained in above Appendix on general considerations (see point ii for weight of evidence therein) characterisation of the analogue substance(s) and a reasoning needs to be provided to establish why information from analogue substance(s) can reliably contribute to the WoE. ECHA notes that the report you have provided does not include:

- detailed information on the identity of the analogue substance(s); in particular the composition of the test material(s);
- any reasoning establishing why information from analogue substance(s) can reliably contribute to the WoE;
- any experimental study summaries for the studies on analogue substance(s) that would allow to assess whether the studies are relevant and reliable.

Therefore, you have not established why the QSAR Toolbox report constitutes a relevant source of information and can reliably contribute to a weight of evidence adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

Regarding the information under point (ii), you have disregarded the study by assigning a reliability score of 4 to the reported study. ECHA agrees that the documentation provided for this study does not allow to assess its reliability. Therefore ECHA cannot consider the report a reliable source of information contributing to weight of evidence for the presence or absence of the particular dangerous property. Furthermore the provided study would not fulfil the requirements of an OECD TG 471 study (updated 1997) on its own, because the study does not include tests with strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). One of these strains is a key parameter required in the current OECD TG 471

(1997). Therefore, the study does not provide all the data required in an OECD TG 471 study.

As explained above, ECHA identified deficiencies in the reliability and relevance of the submitted information. You have not provided documentation to your WoE approach which would include an assessment of relative weights of the individual pieces of information and the subsequent conclusions drawn. In conclusion, there is not sufficient evidence, based on any source of information alone or considered together that the Substance does or does not cause mutations in bacteria. Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

Appendix C: Reasons for the requests to comply with Annex VIII of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to the REACH Regulation.

1. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

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

You have provided one endpoint study record for this information requirement; an automated report generated with the OECD QSAR Toolbox.

You indicated "(Q)SAR" in the administrative section of the endpoint study record and you flagged the adequacy of the study as "weight-of-evidence". However, since you have provided only one endpoint study record for this endpoint, by definition, this is not a weight-of-evidence adaptation under Annex XI, Section 1.2. The QSAR toolbox report moreover states that it is used to predict chromosomal aberration for the Substance based on read-across from analogue substances. It is from this information that ECHA understands that you have sought to adapt the standard information requirement according to Annex XI, Section 1.5 Grouping and read-across.

The conditions for adapting the standard information under the general rules are further explained in the Appendix on general considerations above.

For the use of read-across adaptation under Annex XI, Section 1.5., the cumulative conditions set out under the Appendix on General considerations, point (iv) above, must be necessarily fulfilled. Regarding the provided information, ECHA notes the following:

- The documentation does not include a detailed assessment of the structural similarities and dissimilarities between the Substance and the proposed analogue(s); it also lacks a read-across hypothesis establishing why the results generated with the source substance(s) can be used to predict the results for the target substance;
- There are further no experimental study records neither with the Substance nor with structurally similar analogue(s) which would substantiate the prediction. Absence of experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across.

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An *In vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to the REACH Regulation, if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained.

The registration dossier does not contain any appropriate study record Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2., as explained above under B.1 and C.1. Provided that

the studies requested under B.1 and C.1 have negative results, information on *In vitro* gene mutation in mammalian cells will need to be provided in the dossier.

You have provided two endpoint study records, *in vitro* gene mutation study in mammalian cells and *in vitro* DNA damage and/or repair study. You have indicated "calculation" and flagged the adequacy of the studies as "weight-of-evidence" in the administrative section of the endpoint study records. Hence ECHA understands that you have sought to adapt the standard information requirement according to Annex XI, Section 1.2 Weight of evidence.

The conditions for adapting the standard information under the general rules are further explained in the Appendix on general considerations above.

For both studies, you indicate a calculation using a Multicase model. In order to consider the information as part of a weight of evidence adaptation, reliability of the calculations would need to be demonstrated using the conditions for QSARs explained in above Appendix on general considerations (point iii therein). ECHA notes that you have not provided any documentation that would contain:

- An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
- An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction, and
- An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

Therefore, you have not established why the QSAR predictions constitute relevant sources of information and can reliably contribute to a weight of evidence adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

Furthermore you have not provided documentation to your WoE approach which would include an assessment of relative weights of the individual pieces of information and the subsequent conclusions drawn.

In conclusion, there is not sufficient evidence, based on any source of information alone or considered together that the Substance does or does not cause mutations in mammalian cells. Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

Screening for reproductive/developmental toxicity (test method OECD TG 421 or 422) is a standard information requirement under Annex VIII to the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier.

You have adapted the standard information under Annex XI, Section 1.2., Weight of evidence, by providing the following information and indicated the adequacy of the studies as "weight-of-evidence":

(i) Sub-chronic (90-day) study in rats, inhalation route, similar to OECD TG 452, no GLP compliance, with the Substance;

(ii) You have indicated "(Q)SAR" in the administrative section of one endpoint study record in the technical dossier for this endpoint. In the technical dossier you provided an automated report generated with the OECD QSAR Toolbox.

In addition, you have provided the following information and indicated the studies (iii) – (v) as "weight-of-evidence" but flagged them as "RA" and "WoE".

With the substance 2-(2-ethoxyethoxy)ethanol (EC number 203-919-7; CAS RN 111-90-0):

(iii) Sub-chronic (90-day) dietary toxicity study in rats (publication titled "Short-term toxicity of diethyleneglycol monoethylether in the rat, mouse and pig", 1968, no guideline specified, no GLP compliance)

(iv) Sub-chronic (90-day) dietary toxicity study in pigs (the same publication as in (iii)

With the substance 2-ethoxyethyl acetate (EC number 203-839-2; CAS RN 111-15-9)

(v) Two-generation reproductive toxicity study in mice ([redacted] study titled "Ethylene Glycol Monoethyl Ether Acetate Reproduction and Fertility Assessment in CD-1 mice when administered in drinking water", 1985, GLP not specified).

ECHA has evaluated the provided information (i-v) and notes the following:

(i) The sub-chronic toxicity study (similar to OECD TG 452) does not provide alone the information required by Annex VIII, Section 8.7.1., because it does not cover key parameters of reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition.

(ii) The QSAR toolbox report you submitted states that it is used to predict reproductive toxicity NOAEL for the Substance based on read-across from analogue substances.
Therefore, as explained in above Appendix on general considerations (point ii on Weight of evidence therein) characterisation of the analogue substance(s) and a reasoning needs to be provided to establish why information from analogue substance(s) can reliably contribute to the WoE. For the same reasons explained in Appendices B.1 and C.1, you have not established why the QSAR Toolbox report constitutes a relevant source of information and can reliably contribute to a weight of evidence adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

(iii)-(v) First, as explained in above Appendix on general considerations (point ii on Weight of evidence therein), characterisation of the analogue substance(s) and a reasoning needs to be provided to establish why information from analogue substance(s) can reliably contribute to the WoE. ECHA notes that you have not provided:

- detailed information on the identity of the source substance(s) in particular the composition of the test material(s);
- any reasoning establishing why information from analogue substance(s) can reliably contribute to the WoE.

Second, for the studies (iii) and (iv), for the same reasons as stated for study (i) above, a 90-day repeated dose toxicity study does not provide relevant information to predict the reproductive/developmental properties as required by Annex VIII, Section 8.7.1.

Third, the GLP status of some of the studies is identified as "no GLP" or "GLP not specified". The uncertainty of the conditions under which the studies have

been conducted affects the assessment of the reliability of this information. Reliability is an important parameter of the WoE, as explained in point (ii) of the General considerations. You have not explained how this limitation affects the use of this information as part of the WoE approach.

Fourth, ECHA notes that the analogue substance 2-ethoxyethyl acetate, tested in study (v) included in your WoE approach, has a harmonised classification as Repro 1B (H360FD). ECHA points out that you have not explained in your weight of evidence argumentation why you consider that information from this analogue substance is relevant for the WoE whilst concluding that the Substance does not have reproductive toxicity properties also warranting classification as Repro 1B.

In conclusion, you have not established why the studies on the analogue substances constitute relevant information and can reliably contribute to a weight of evidence adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

As explained above, ECHA identified deficiencies in the reliability and relevance of the submitted information. You have further not provided documentation to your WoE approach which would include an assessment of relative weights of the individual pieces of information and the subsequent conclusions drawn. In conclusion, there is not sufficient evidence, based on any source of information alone or considered together that the Substance is or is not toxic to reproduction or a developmental toxicant. Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

According to the test method OECD TG 421/422 testing should be performed with rats. The oral route is the most relevant route of administration to investigate reproductive toxicity (ECHA Guidance R.7a). The study shall be performed by the oral route.

Appendix D: Reasons for the requests to comply with Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to the REACH Regulation.

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species;**

A Pre-natal developmental toxicity study for a first species is a standard information requirement under Annex IX to the REACH Regulation.

You have adapted the standard information requirement according to Annex XI, Section 1.2., Weight of evidence, by providing the following information and indicated the adequacy of the studies as "weight-of-evidence":

(i) You have indicated "(Q)SAR" in the administrative section of one endpoint study record in the technical dossier for this endpoint. In the technical dossier you provided an automated report generated with the OECD QSAR Toolbox indicating that it is used to estimate LOEL for foetotoxicity based on weight of evidence "*from 5 nearest neighbours*".

(ii) You have indicated "calculation" in the administrative section of the endpoint study record in the technical dossier for developmental toxicity. You indicate a calculation using a Multicase model.

You have also provided studies performed with proposed analogue substances and indicated them as "weight-of-evidence", as follows:

For the substance 2-(2-ethoxyethoxy)ethanol (EC number 203-919-7: CAS RN 111-90-0):

(iii) A publication titled "Developmental toxicity of 4 glycol ethers applied cutaneously to rats", 1984, claimed to be similar to OECD TG 414, GLP not specified.

For the substance 2-ethoxyethyl acetate (EC number 203-839-2: CAS RN 111-15-9):

(iv) Developmental toxicity study (inhalation, vapour) in rats (publication titled "Developmental toxicity evaluation of inhaled 2-ethoxyethanol acetate in Fischer 344 rats and New Zealand white rabbits", 1988, no guideline specified, not GLP compliant).

(v) Developmental toxicity study (inhalation, vapour) in rabbits (the same publication as in (iv)

ECHA has evaluated the provided information (i-v) and notes the following:

(i) The QSAR toolbox report states that it is used to predict foetotoxicity for the Substance based on read-across from analogue substances. Therefore, as explained in above Appendix on general considerations (point ii on Weight of evidence therein), characterisation of the analogue substance(s) and a reasoning needs to be provided to establish why information from analogue substance(s) can reliably contribute to the WoE. For the same reasons as explained in Appendices B.1 and C.1, you have not established why the QSAR Toolbox report constitutes a relevant source of information and can reliably contribute to a weight of evidence adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

(ii) In order to consider the calculation as part of the weight of evidence adaptation, reliability of the prediction would need to be demonstrated by fulfilling the

conditions for QSARs in Appendix on general considerations (point iii therein) above. ECHA notes that you have not provided any documentation that would contain:

- An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
- An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction, and
- An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

ECHA also notes that it is currently not aware of any scientifically valid QSAR models that could reliably predict the outcome of experimental tests for this endpoint.

Therefore, you have not established why the QSAR predictions constitute relevant sources of information and can reliably contribute to a weight of evidence adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

(iii-v) As explained in above Appendix on general considerations (point ii on Weight of evidence therein) characterisation of the analogue substance(s) and a reasoning needs to be provided to establish why information from analogue substance(s) can reliably contribute to the WoE. ECHA notes that you have not provided:

- detailed information on the identity of the source substance(s) in particular the composition of the test material(s);
- any reasoning establishing why information from analogue substance(s) can reliably contribute to the WoE;

In addition, the GLP status of some of the studies is identified as "no GLP" or "GLP not specified". The uncertainty of the conditions under which the studies have been conducted affects the assessment of the reliability of this information. Reliability is an important parameter of the WoE, as explained in point (ii) of the Appendix on general considerations above. You have not explained how this limitation affects the use of this information as part of the WoE approach.

Further, the analogue substance 2-ethoxyethyl acetate, tested in studies (iv) and (v) included in your WoE approach, has a harmonised classification as Repro 1B (H360FD). In spite of this, you conclude that the Substance does not have reproductive toxicity properties also warranting classification as Repro 1B. You have not explained in your argumentation why you did not take account of that relevant information on this analogue substance for the WoE.

As explained above, ECHA identified deficiencies in the reliability and relevance of the submitted information. You have further not provided documentation to your WoE approach which would include an assessment of relative weights of the individual pieces of information and the subsequent conclusions drawn. In conclusion, there is not sufficient evidence, based on any source of information alone or considered together that the Substance is or is not a developmental toxicant. Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

According to the test method OECD TG 414 testing should be performed with rats or rabbits. The oral route is the most relevant route of administration to investigate reproductive toxicity (ECHA Guidance R.7a). The study shall be performed by the oral route.

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.);

Long-term toxicity testing on fish is a standard information requirement under Annex IX to the REACH Regulation.

You have adapted this information requirement with the following justification: *"According to column I of annex IX , Long-term toxicity testing on fish need not to be conducted as it is already provided as part of Annex VIII requirements. Also the substance 2-(2-ethoxyethoxy)ethyl acetate is found to be readily biodegradable. Therefore this study was considered to be waived."*

You provided results from four experimental toxicity tests on fish as part of IUCLID section 6.1.1. Short-term toxicity to fish (Annex VIII requirement). The duration of these tests were 96-h or 7-d and the observed endpoint was mortality.

According to ECHA Guidance R.7b, only studies where sensitive life-stages (juveniles, eggs, larvae) are exposed to the test material can be regarded as long-term fish test. Observational endpoints include hatching success, survival and growth. The required test duration varies from 60 days post-hatch for rainbow trout to 30 days for warm water fish.

The 96-h and 7-d toxicity studies provided on fish lethality have too short exposure period to the test material and observational endpoints did not include hatching success, survival and growth. Therefore they cannot be considered as long-term studies.

In your adaptation you also state that the substance is readily biodegradable. You have not further justified why ready biodegradability allows you to adapt this information requirement. According to Annex IX section 9.1 and ECHA Guidance R.7b section R.7.8.4.3, substance's biodegradability is not itself a justified reason to adapt this information requirement.

In conclusion your adaptation is rejected.

You have also provided information from a calculation (ECOSAR v1.11 developed by USEPA).

ECHA has evaluated this information under Annex XI, Section 1.3, and the conditions specified in the Appendix on general considerations above (point iii therein).
ECHA notes that you have not provided any documentation containing:

1. An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
2. An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction, and
3. An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

On this basis, ECHA concludes that the proposed adaptation is not in line with the conditions specified in Annex XI, Section 1.3. and therefore rejects it. Consequently, the information requirement is not fulfilled.

Appendix E: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 20 July 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments and referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-66 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix F: Observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test material

   Selection and technical reporting of the test material(s)

   It is the responsibility of all registrants of the Substance to agree on the composition of the test material in carrying out the tests required by the present decision. It is important to select the test material so that it is relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have 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 shall contain that constituent/impurity.

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website (https://echa.europa.eu/manuals).

4. List of references for the Guidance documents referred to in this decision

   Evaluation of available information
   Guidance on information requirements and chemical safety assessment, Chapter R.4.4 (version 1.1, December 2011): referred to as ECHA Guidance R.4.4 in this decision.

   QSAR predictions

   Guidance on information requirements and chemical safety assessment, Chapter R.6.1 (version 1.0, May 2008), referred to as ECHA Guidance R.6.1 in this decision.

   Read-across and grouping

   Guidance on information requirements and chemical safety assessment, Chapter R.6.2 (version 1.0, May 2008), referred to as ECHA Guidance R.6.2 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.

5. Test guidelines, GLP requirements and reporting

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

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

According to 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 3: 'How to report robust study summaries'.

Appendix G: List of the registrants to which the decision is a addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	Data requirements to be fufilled
[redacted]	[redacted]	[redacted]