~~Confidential~~

Helsinki, 22 October 2020

Addressees
Registrant(s) of TEGBE GE consortium as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
10 December 2019

Registered substance subject to this decision ("the Substance")
Substance name: 2-(2-(2-butoxyethoxy)ethoxy)ethanol
EC number: 205-592-6
CAS number: 143-22-6

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***29 April 2022***.

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

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

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

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

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

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

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

Information required depends on your tonnage band

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

- the information specified in Annexes VII, and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa; and
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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

How to comply with your information requirements

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

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

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 Christel Schilliger-Musset, Director of Hazard Assessment

[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 A: Reasons to request information required under Annex VIII of REACH

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

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

You have provided dermal short-term (21-day) toxicity study (i; OECD TG 410) in rabbits conducted with the Substance (Leber et al, 1990).

In addition, you have provided the following studies with the structurally similar substance 2-(2-(2-methoxyethoxy)ethoxy)ethanol (TEGME; EC no 203-962-1):

ii. Oral sub-chronic (90-day) toxicity study ([redacted], 1990d); and
iii. Dermal sub-chronic (90-day) toxicity study ([redacted] 1990e).

We have assessed this information and identified the following issues:

A. The objective of assessing repeated dose toxicity includes evaluating whether administration of a substance to animals causes local and systemic adverse toxicological effects as a result of repeated daily exposure.[2] Repeated dose toxicity studies must be performed by either the oral, inhalation or dermal route. Referring to the criteria in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because it is assumed to maximise systemic availability of most substances[3]. Testing for repeated dose toxicity by the dermal route is appropriate if skin contact with the substance in production and/or use is likely and the physico-chemical properties suggest a potential for a significant rate of absorption through the skin.[4]

   You have provided a short-term toxicity study (i) conducted with the Substance. In this study, the Substance was delivered to rabbits via the dermal route.

   Based on the rate of diffusion across human skin of 22 µg/cm^2/hr measured in the *in vitro* dermal absorption assay provided in your dossier, the permeability of the Substance to human skin is quite low. There is no information provided in the dossier to indicate that the permeability to rabbit skin is significantly higher than to human skin. Therefore, administration of the test item via the dermal route is not expected to maximise systemic exposure and data obtained from studies conducted via the dermal route may lead to an underestimation of the properties of the Substance and therefore cannot be used for hazard identification and risk assessment purposes.

   In conclusion, the dermal route is not considered as the most appropriate route to test for repeated dose toxicity in the context of REACH, and therefore, the provided study (i) conducted with the Substance cannot be used to fulfil this information requirement.

[2] ECHA Guidance R.7a, Section R.7.5.1.2
[3] ECHA Guidance R.7a, Section R.7.5.4.3.2
[4] ECHA Guidance R.7a, Section R.7.5.6.3.4

B. As provided in Annex VIII, Section 8.6.1, Column 2, you may adapt the information requirement, provided a reliable sub-chronic toxicity study (90-day) is available with the appropriate species, dosage, solvent and route of administration.

You have provided sub-chronic (90-day) oral (ii) and dermal (iii) studies conducted with the analogue substance TEGME.

As explained in Appendix B, section 1 your read-across approach is rejected, and therefore, the information from the analogue substances is not considered reliable.

In addition, as noted in point A above, dermal route of administration is not considered as the most appropriate route to test for repeated dose toxicity in the context of REACH, and therefore, the provided study (iii) is not considered reliable.

As a conclusion, no reliable sub-chronic toxicity studies are available, and therefore, the conditions for the adaptation are not fulfilled and your adaptation is rejected.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Section B.1). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted.

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

In your comments on the draft decision, you agree to provide the justification as specified in the decision.

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

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

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

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5 using the following:

You have provided oral sub-chronic toxicity study ([redacted], 1990d) conducted with the structurally similar substance 2-(2-(2-methoxyethoxy)ethoxy)ethanol (TEGME; EC no 203-962-1).

We have assessed this information and identified the following issues:

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.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

A. Scope of the grouping

In your registration dossier you have formed a group (category) of 'E series glycol ether heavies'. You have provided a read-across justification in CSR and in the category justification document in IUCLID.

For the purpose of this decision, the following abbreviations are used for the group members:

[1] Triethylene glycol monomethyl ether (TEGME; EC no 203-962-1)
[2] Tetraethylene glycol monomethyl ether (TetraEGME; EC no 245-883-5)
[3] Triethylene glycol monoethyl ether (TEGEE; EC no 203-978-9)
[4] Triethylene glycol monobutyl ether (TEGBE; EC no 205-592-6)
[5] Tetraethylene glycol monobutyl ether (TetraEGBE; EC no 216-322-1)
[6] Reaction mass of 3,6,9,12-tetraoxatridecan-1-ol and 3,6,9,12,15-pentaoxahexadecan-1-ol (TetraEGMe-PentaEGME; EC no 915-389-0)
[7] Reaction mass of 2-(2-(2-butoxyethoxy)ethoxy)ethanol and 3,6,9,12-tetraoxahexadecan-1-ol (TEGBE-TetraEGBE; EC no 907-996-4)
[8] Poly(oxy-1,2-ethandiyl), α-butyl-ω-hydroxyl (NLPBuH; EC no 500-012-0)

You provide the following reasoning for the grouping the substances: "*This category covers E series glycol ethers that are produced by the reaction of ethylene oxide (EO) with primary alcohols in the range C1-C4 (methanol to butanol) and that contain three or more ethylene oxide oligomeric units, although the number for discrete molecules (mono-and multi-constituent substances) is three to five".*

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

B. Predictions for properties

You have provided the following reasoning for the prediction of toxicological properties: *"The hypothesis is that members of this category follow similar metabolic pathways, with the main metabolite derived through oxidation of the hydroxyl function to a carboxylate group and that, for systemic end points, the acid metabolite primarily determines the toxicity of the glycol ether rather than the parent glycol ether itself. A key assumption is that the substances all show the same (low) toxicity properties".*

In addition, according to the information provided on pages 27 and 35 of your category justification document, for the endpoint repeated-dose toxicity, your hypothesis is that there is data suggesting that "*toxicity decreases with increasing alkyl chain length*" and "*toxicity decreases down each homologous series with increasing number of EO units*", respectively. ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of the category members, including the Substance, are predicted based on a worst-case approach, as toxicity is expected to decrease with increasing alkyl chain length and decrease down each homologous series with increasing number of EO units.

You intend to predict the relevant property of the Substance from the sub-chronic oral toxicity study conducted with the source substance TEGME ([redacted], 1990d).

The source substance TEGME and the Substance contain the shortest (C1) and longest (C4) alkyl chain lengths in the category, respectively. In addition, both substances contain the lowest number of EO units (three) while in the category there are members with the higher number or EO units. According to your read-across hypothesis, the source substance TEGME and the Substance are assumed to be the most toxic substances of the methyl and butyl alkyl series, respectively. As indicated above, these series corresponds to the alkyl chain length boundaries of the category.

ECHA notes the following shortcomings with regards to the predictions of toxicological properties.

Missing information to support hypothesis

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[5]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on other category members.

As indicated above, your read-across hypothesis is based on the assumption that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance because the toxicity is expected to decrease with increasing alkyl chain length and decrease down each homologous series with increasing number of EO units.

In this context, relevant, reliable and adequate information allowing to compare the properties of the category members is necessary to confirm a conservative prediction of the properties

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

of the Substance from the data on other category members. Such information can be obtained, for example, from bridging studies of comparable design and duration for the category members.

To support your hypothesis you have provided dermal sub-chronic toxicity (90-day) study in rats conducted with the source substance TEGME ([redacted] 1990e) and short-term dermal toxicity (21-day) study in rabbits conducted with the Substance (Leber et al, 1990). In addition, you have provided toxicokinetic data for the source substance TEGME and the Substance to evaluate the metabolic pathways of these substances (category justification and Bogaards et al., 2017). Furthermore, you have indicated your intention to conduct a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to the OECD TG 422 on another category member TEGBE-TetraEGBE (EC no 907-996-4). This susbstance belongs to the same butyl alkyl series as the Substance but in addition to three EO units also contains butyl ether with four EO units compared to only three EO units present in the Substance.

First, dermal repeat dose toxicity studies that you provided are not a reliable basis as bridging information to support your read-across hypothesis as dermal route is not appropriate to evaluate the repeat dose toxicity (explained in appendix A, section 1) and no information is available to allow evaluation that the systemic exposure following dermal administration of the substances is comparable.

Second, the *in vivo* toxiokinetic data that you have provided for the Substance and the source substance TEGME shows differences in the relative importance of the different metabolic pathways as alkyl chain length increases. This can lead to differences in the relative proportions of metabolites following exposure to the Substance and the source Substance. As explained above, you have not provided reliable comparable data with the Substance and source substance to evaluate the impact of the differences in the metabolic pathways on the hazard properties of the substances.

Third, you have not provided any information to support part of your hypothesis that considers that "*toxicity decreases down each homologous series with increasing number of ethylene oxide (EO) units*". Although this deficiency does not add to the failure of the read-across between your Substance and the source substance (as they have the same three EO units), it matters for other category members and ECHA provides some considerations. Specifically, your plan in the dossier subject to compliance check to conduct a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to the OECD TG 422 on another category member TEGBE-TetraEGBE (EC no 907-996-4) may or may not support your hypothesis, depending on the result obtained and on the availability of repeated-dose toxicity data for the butyl alkyl series (with lower number of EO within the butyl series) to allow comparison. In particular, a sub-chronic toxicity study conducted with the Substance, as requested in the current decision (hypothesised to be the most toxic member of the category in the butyl alkyl series) could enable such comparison.

Based on your comments, ECHA understands that you wish to take into account the results obtained from the requested sub-chronic toxicity study before deciding on the appropriate additional study to be performed to support the category. While this is in your discretion, if you continue with the hypothesis that 'toxicity decreases down the homologous series with increasing number of ethylene oxide (EO) units', ECHA stresses that information on repeated-dose toxicity data with higher number of EO units within the butyl series is needed to allow comparison of repeated-dose toxicity data within the butyl alkyl series.

As a conclusion, in the absence of reliable supporting studies, you have not established that the source substance TEGME constitutes a worst-case for the prediction of the property under consideration of the other category members, and most specifically your Substance. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Adequacy and reliability of source study

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

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

OECD TG 408 is the preferred/corresponding guideline to fulfi this information requirement and the coverage of the following key parameters is required, among others

- Recording of haematology and clinical biochemistry; and
- Full detailed gross necropsy and subsequent histopathology of tissues such as heart, pituitary, thyroid/parathyroid, thymus, and uterus.

The provided study was not performed according to the criteria of the OECD TG 408. The study does not have the required recording of haematology and clinical biochemistry or the full detailed gross necropsy and subsequent histopathology of tissues such as pituitary, thyroid/parathyroid, thymus, and uterus.

The sub-chronic oral study provided in your dossier does not provide an adequate coverage the key parameters specified above and expected to be investigated in a study on sub-chronic toxicity study (90-day). Therefore, this study is not adequate for the purpose of classification and labelling and/or risk assessment.

C. Conclusion

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., and your adaptation is rejected.

Therefore, the information requirement is not fulfilled.

Information on the design of the study to be performed

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity and the prefered rodent species is rat[6].

The sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

In your comments on the draft decision you agree to conduct the requested test as specified in the decision. You further provided information on the study design to comply with the decision. The study design is in your discretion as long as you comply with the relevant test guideline and do not jeopardise the validity of the study.

[6] ECHA Guidance R.7a, Section R.7.5.6.3.2 and Table R.7.5-1

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

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[7].

B. Test material

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

1. Selection of the Test material(s)

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

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[8].

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

Appendix D: 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 17 October 2019.

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

ECHA took into account your comments and amended the deadline.

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested information was 12 months from the date of adoption of the decision.

In your comments to the draft decision you requested ECHA to extend the standard granted time by 3 to 6 months to a total of 15 to 18 months based on the additional time required to complete the testing and compile the necessary information for a dossier update. Based on the documentary evidence provided, ECHA has agreed with your request for a deadline extension and granted 3 months extension to the original deadline. Therefore, the deadline is set to 15 months.

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

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

Appendix E: List of references - ECHA Guidance[9] and other supporting documents

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

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

Read-across assessment framework (RAAF, March 2017)[10]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[10]

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

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

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

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

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

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

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

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

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

OECD Guidance documents[11]

[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

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

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

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

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

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

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

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