~~Confidential~~

Helsinki, 22 October 2020

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

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

Registered substance subject to this decision ("the Substance")
Substance name: 2-(2-(2-METHOXYETHOXY)ETHOXY)ETHANOL
EC number: 203-962-1
CAS number: 112-35-6

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 appendix:

- Appendix 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 the following studies conducted with the Substance:

i. Subchronic oral (90-day) toxicity study (OECD TG 408) in rats ([redacted], 1990) as key study;
ii. Subchronic dermal (90-day) toxicity study (OECD TG 411) in rats ([redacted], 1990) as key study; and
iii. Short-term dermal toxicity study, with the exposure duration of 21 day (OECD TG 410) in rabbits (Leber, 1990) as supporting study.

We have assessed this information and identified the following issues:

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

   You have provided subchronic oral (i) and dermal (ii) toxicity studies in rats as key studies. Therefore, while you have not provided a justification, ECHA has evaluated the provided information according to Annex VIII, Section 8.6.1, Column 2.

   As explained in point B.1 below, the repeated dose toxicity studies (i-ii) you provided are not considered compliant.

   In particular, for oral subchronic toxicity study (i) you failed to provide information on haematology and clinical biochemistry as well as full detailed gross necropsy and histopathology of organs such as heart, pituitary, thyroid/parathyroid, thymus, and uterus (B.1.A). On the other hand, the dermal route is not appropriate to evaluate the repeat dose toxicity (B.1.B) in the sub-chronic (ii).

   As no reliable sub-chronic toxicity study, and on the appropriate route of administration, is provided, the conditions for the adaptation are not fulfilled and your adaptation is rejected.

   B. 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 VIII, Section 8.6.1, 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

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

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 dermal short-term toxicity study in rabbits (iii) as supporting study. As explained below under point B.1.B, dermal route is not appropriate to evaluate the repeat dose toxicity. Therefore, the information you provided do not fulfil the information requirement.

Based on the above, the information requirement is not fulfilled.

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.

[4] ECHA Guidance R.7a, Section R.7.5.6.3.4

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

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

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

You have provided following studies conducted with the Substance:

i. Subchronic oral (90-day) toxicity study (OECD TG 408) in rats ([redacted], 1990) as key study;
ii. Subchronic dermal (90-day) toxicity study (OECD TG 411) in rats ([redacted], 1990) as key study; and
iii. Short-term dermal toxicity (21/28-day) study (OECD TG 410) in rabbits (Leber, 1990) as supporting study.

We have assessed this information and identified the following issues:

A. To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408 (oral) or of the OECD TG 411 (dermal). The following key parameter(s) of this test guideline include, among others
   - Recording of haematology and clinical biochemistry;
   - Full detailed gross necropsy and subsequent histopathology of tissues such as heart, pituitary, thyroid/parathyroid, thymus, and uterus; and
   - dosing of the Substance daily for a period of 90 days until the scheduled termination of the study.

   The provided study (i) 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 provided study (iii) does not have the required exposure duration of 90 days as required in OECD TG 411, because you indicated an exposure duration of 21 days.

   Therefore, the studies (i) and (iii) do not fulfil the criterion set in OECD TG 408 and OECD TG 411, respectively.

B. 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.[5] 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[6]. 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.[7]

[5] ECHA Guidance R.7a, Section R.7.5.1.2
[6] ECHA Guidance R.7a, Section R.7.5.4.3.2
[7] ECHA Guidance R.7a, Section R.7.5.6.3.4

You have provided a 90-day (ii) and 21-day (iii) repeated dose toxicity studies in which the Substance was delivered to rats or rabbits, respectively, via the dermal route. Based on the rate of diffusion across human skin of 34 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 rat/rabbit skin is significantly higher than to human skin. Furthermore, dose-related increases in mean liver weight were observed for male rats in all three treatment groups (420, 1200, 4000 mg/kg bw/d) following oral exposure to the Substance for 90 days. However, no changes in liver weights were reported in the provided dermal 90-day rat study (doses up to 4000 mg/kg bw/d). This indicates that administration of the Substance to rats via the oral route leads to a higher systemic exposure to the Substance than administration via the dermal route. Therefore, administration of the test item via the dermal route does not 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 studies (ii, iii) cannot be used to fulfil this information requirement.

As described above, the provided studies are rejected and 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[8].

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.

Further observations

In your comments you also indicate that there is currently a testing proposal under consideration for the Substance for the Extended one-generation reproductive toxicity study (EOGRTS) (OECD TG 443). You request that the examination of this testing proposal is postponed until the information from the sub-chronic toxicity study requested in this decision is available. ECHA confirms that the testing proposal for the EOGRTS will only be examined once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is available.

[8] 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[9].

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[10].

[9] https://echa.europa.eu/practical-guides
[10] 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[11] 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)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[12]

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[13]

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

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]
[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.