~~Confidential~~

Helsinki, 04 November 2020

Addressees
Registrant(s) of JS_Bis(2-ethoxyethyl)ether as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
26 March 2013

Registered substance subject to this decision ("the Substance")
Substance name: Bis(2-ethoxyethyl) ether
EC number: 203-963-7
CAS number: 112-36-7

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 ***9 August 2022***.

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

A. 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 Annex IX of REACH".

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, VIII and IX to REACH, for registration at 100-1000 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 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 adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support of your adaptation, you have provided the following sources of information:

Studies conducted with the Substance

i. Short-term inhalation toxicity study (28-day) ([redacted], 2013), Key study
ii. Short-term inhalation toxicity study (28-day) (Gage et al., 1970)

Studies conducted with analogue substances

iii. Sub-chronic oral (diet) toxicity study (90-day) conducted with diethyleneglycol ethyl ether (DEGEE, EC No. 203-919-7) (Hall et al, 1965)
iv. Sub-chronic oral (diet) toxicity study (90-day) conducted with DEGEE (Gaunt et al., 1968)
v. Short-term inhalation toxicity study (28-day) conducted with DEGEE (Hardy et al., 1997)
vi. Short-term dermal toxicity study (30-day) conducted with DEGEE (Hanzlik et al., 1947)
vii. Sub-chronic dermal toxicity study (90-day) conducted with diethyleneglycol methyl ether (DEGME) (Hobson et al., 1986)
viii. Short-term dermal toxicity study (Screening study) conducted with diethyleneglycol butyl ether (DEGBE, EC No. 203-961-6) (Auletta et al., 1993)
ix. Sub-chronic oral (drinking water) toxicity study (90-day) conducted with DEGBE (Johnson et al., 2004)
x. Sub-chronic dermal toxicity study (90-day) conducted DEGBE (Beyrouty et al., 1993)
xi. Short-term oral (gavage) toxicity study (20-day) conducted with diethyleneglycol dimethyl ether (DEGDME, EC No. 203-924-4) (Cheever et al., 1989)
xii. Sub-chronic inhalation toxicity study (90-day) conducted with DEGDME, EC No. 203-924-4) (Valentine et al., 1999)

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the sub-chronic toxicity (90-day) of the Substance.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

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

sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes, at general level, information on systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system.

You have provided several repeated dose toxicity studies conducted with either the Substance (i, ii) or the analogue substances (iii-xii). These source(s) of information provide relevant information for sub-chronic toxicity, but have the following deficiencies affecting their contribution to the derivation of reliable conclusions:

1. *Information on studies conducted with the Substance*

The conditions of exposure in accordance with the OECD TG 408 specifies that dosing of the Substance is performed daily for a period of 90 days until the scheduled termination of the study.

You have provided two 28-day inhalation toxicity studies (i - ii) conducted with the Substance. These studies do not have the the exposure duration of 90 days as required in OECD TG 408.

This condition of exposure is essential, as the effects observed in a sub-chronic study might be considerably more pronounced compared to a shorter study duration such as a 28-day study. You have not demonstrated that the effects of the Substance generated over the exposure of 90 days will not be different to that over the exposure of 28 days. Therefore these studies (i) and (ii) do not inform on the properties of the Substance after a longer exposure than 28 days.

2. *Information on studies conducted with analogue substances*

You have provided several repeated dose toxicity studies conducted with analogue substances.

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under sections 2.a and 2.b below).

Additional information on what is necessary when justifying a read-across approach can be

found in the ECHA Guidance[2] and related documents[3, 4].

In your registration dossier you have formed a category comprising following diethylene glycol mono- and di-alkyl ethers:

[1] Diethyleneglycol methyl ether (DEGME, EC No. 203-906-6);
[2] Diethyleneglycol ethyl ether (DEGEE, EC No. 203-919-7);
[3] Diethyleneglycol dimethyl ether (DEGDME, EC No. 203-924-4);
[4] Diethyleneglycol ethyl methyl ether (DEGMEE, EC No. 213-690-5);
[5] Diethyleneglycol diethyl ether (DEGDEE, EC No. 203-963-7; i.e. the Substance); and
[6] Diethyleneglycol butyl ether (DEGBE, EC No. 203-961-6).

You propose that the target organs and the severity of the toxic effects of glycol ethers including the Substance are dependent on the metabolites produced. The biotransformation of DEGME, DEGDME, DEGEE, DEGDEE and DEGBE results in the ether cleavage and formation of alkoxyacetic acids such as methoxyacetic acid (MAA), ethoxycacetic acid (EAA) and buthoxyacetic acid (BAA), respectively.

For the toxicity profile, you specify that "*the metabolites MAA, EAA and BAA act on different organs: BAA has a haemolytic effect on peripheral blood while MAA and EAA have detrimental effects on the haematopoietic system, the testes and foetus development.*" In addition, you indicate that the dialkyl ethers (such as the Substance) are metabolised differently to the monoalkyl ethers such as category members DEGEE, DEGBE and DEGME. You state that "*The main route of metabolism of diethylene glycol monoalkyl ethers is the oxidation by the alcohol and aldehyde dehydrogenase into alkoxyethoxyacetic acids. A second minor oxidative pathway involves ether cleavage by monooxygenase and formation of alkoxyethanol then oxidation by the alcohol and aldehyde dehydrogenase into alkoxyacetic acids.*" In contrals, "*Diethylene glycol dialkyl ethers with both alcohol groups etherified are metabolised by cleavage of the ether bonds by monooxygenase to form either alkoxyethoxyethanols or alkoxyethanols which are then oxidised by the alcohol and aldehyde dehydrogenase into alkoxyethoxyacetic acids and alkoxyacetic acids*".

For severity of the effects, you hypothesise that the accumulation of the metabolite following frequent exposures to the glycol ethers is likely to be more extensive for MAA generated from category member DEGDME compared with EAA generated from category member DEGEE and expected to be generated from the Substance. This is based on the higher clearance of the metabolite EAA compared to MAA as shown in the toxicokinetic study for EAA and MAA metabolites (Aasmoe et al, 1999). You state that "*Therefore the low levels of metabolite EAA and its fast clearance could explain why DEGDEE is not toxic after one or 4 weeks repeated doses while DEGDME is a reproductive and developmental toxicant after two weeks of dosing.*"

Based on above, ECHA understands that your read-across hypothesis is based on the assumptions that

- the toxicity of the glycol ethers is based on the EAA (the Substance, DEGEE), MAA (DEGDME, DEGEE) and BAA (DEGBE) metabolites expected to be generated from the substances; and
- the substances that could be metabolised to EAA, e.g. the Substance, are expected to be less toxic than the substances metabolised to MAA, e.g. DEGDME as a result of a faster clearance of EAA.

[2] ECHA Guidance R.6
[3] Read-Across Assessment Framework (RAAF)
[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs

ECHA notes the following deficiencies with regards to the use of information on the analogue substances for the determination of the sub-chronic toxicity (90-day) of the Substance:

a. Supporting information on DEGBE

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 hypothesis is that the toxicity of the substance is driven by the metabolites formed from these substances. You have identified that "*the target organs and the severity of the toxic effects are dependent on the metabolites produced from the glycol ethers*". In this context it is important to demonstrate that the toxicological properties of the metabolites formed from the source substances, i.e. their target organs and the nature and severity of the effects in these organs, are similar to those of the metabolites formed from the Substance.

The biotransformation of the Substance (DEGDEE) and of the substance DEGBE results in the ether cleavage and formation of alkoxyacetic acids such as ethoxycacetic acid (EAA) and buthoxyacetic acid (BAA), respectively.

You have provided repeated dose toxicity studies conducted with the analogue substance DEGBE (viii-x) which is expected to metabolise to BAA metabolite. You indicate that the BAA metabolite has a haemolytic effect on peripheral blood while metabolite EAA has detrimental effects on the haematopoietic system, the testes and foetus development.

If the metabolites have different toxicity profiles, it seems justified to assume that the toxicity following systemic exposure to DEGBE which is metabolised to BAA will be different to the toxicity profile following exposure to the Substance expected to be metabolised to EAA.

Based on this, the properties for 90-day repeated toxicity of the Substance are expected to be different from that reported for the category member DEGBE, and the information provided with DEGBE cannot contribute to the formation of reliable conclusions on the properties of the Substance in the context of this weight of evidence.

b. Supporting information on DEGEE and DEGME

According to the ECHA Guidance[5] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

As indicated above, your hypothesis is that the toxicity of the substance is driven by the metabolites formed from these substances and that there are certain differences in the metabolism of the mono-alkyl ethers and the di-alkyl ethers. In this context it is important to demonstrate whether such differences do not affect the toxicological properties.

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

To support your hypothesis, you have referenced human monitoring information and toxicokinetic studies in animal models on DEGME, DEGEE and DEGBE (Laitinen et al. 2005, Miller 1987) informing on the metabolites formed from these mono-alkyl ethers. You report from these studies that the respective akoxyethoxyacetic acids were detected whereas the alkoxyacetic acids could not be detected. You conclude from this information that the "*main route of metabolism of diethylene glycol monoalkyl ethers is the oxidation by the alcohol and aldehyde dehydrogenase into alkoxyethoxyacetic acids. A second minor oxidative pathway involves ether cleavage by monooxygenase and formation of alkoxyethanol then oxidation by the alcohol and aldehyde dehydrogenase into alkoxyacetic acids.*"

In contrast with this conclusion you report that diethylene glycol dialkyl ethers "*with both alcohol groups etherified are metabolised by cleavage of the ether bonds by monooxygenase to form either alkoxyethoxyethanols or alkoxyethanols which are then oxidised by the alcohol and aldehyde dehydrogenase into alkoxyethoxyacetic acids and alkoxyacetic acids*". You consider that "*although pharmacokinetic studies with DEGDEE have not been performed, its metabolic fate is expected to be similar to that of DEGDME due to similarities in structure*". In your justification document you state that "*DEGDEE and DEGDME have both alcohol groups etherified while DEGEE, DEGBE and DEGME are etherified at only one OH function, and therefore their metabolism is slightly different.*"

You have provided experimental toxicokinetic information for dialkyl ether DEGDME (Cheever et al., 1988, 1991; Richards et al., 1993) establishing that "*diethylene glycol dialkyl ethers metabolism appears to be much dependent on metabolic status and has a higher capacity following liver enzyme induction thus metabolism is increased by repeated administration*".

As indicated in your justification document, the toxic alkoxyacetic acid metabolites are not generated via the main route of metabolism of mono-alkyl ethers such as DEGEE and DEGME but result from a minor oxidative pathway. Based on the information in the justification document, this oxidative pathway may be more important in the metabolism of di-alkyl ethers, including the Substance. The importance of this pathway even increases after repeated administration as higher capacity for metabolism is expected due to liver enzyme induction, as you indicate in your justification document. Based on above, the formation of the putative toxic alkoxyacetic acid metabolites is therefore expected to be lower for mono-alkyl ethers when compared to di-alkyl ethers. In such a case, information generated with the mono alkyl ethers such as DEGEE and DEGME may underestimate the properties for 90-day repeated toxicity of the Substance.

You have not provided any information establishing that the identified differences in the metabolism do not affect the toxicological properties of the mono- and di-alkyl ethers. Therefore, the information from studies iii-vii provided on mono-alkyl ethers DEGME and DEGEE cannot contribute to the formation of reliable conclusions on the properties of the Substance in the context of this weight of evidence.

3. Integration and weighing of the sources of information

As explained under section 2, you hypothesised that the low toxicity of the Substance following 28-day repeated administration is due to the lower levels and accumulation of EAA compared to that of MAA, and therefore the Substance is expected to be less toxic than DEGDME.

However, you have not addressed the impact of the formation and possible accumulation of EAA following repeated administration of the Substance over 90 days on the properties of the Substance. Whilst you consider that the Substance is less toxic after 90-day repeated

administration than DEGDME, you do not conclude on the type and severity of effects caused by sub-chronic exposure to the Substance. Your consideration that 'the Substance is less toxic' does not address the requirement of Annex XI 1.2 on whether or not the Substance has a particular dangerous property after sub-chronic exposure.

Conclusion

All together, as indicated in sections 1-3 above, there are limitations with information provided in studies i-xii, and lack of consideration on the type and severity of effects caused by sub-chronic exposure to the Substance.

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in a sub-chronic toxicity study.

Therefore, your adaptation is rejected.

In your comments on the draft decision, you agreed with ECHA's assessment.

Appendix B: 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[6].

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[7].

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

Appendix C: 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 6 June 2019.

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

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 D: List of references - ECHA Guidance[8] 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)[9]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[9]

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[10]

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