ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 18 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114363810-52-01/F
Substance name: Diethyl ether
EC number: 200-467-2
CAS number: 60-29-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 25.03.2015
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) in rats with the registered substance;**

3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

4. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **25 July 2019**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

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[1] by Claudio Carlon, Head of Unit, Evaluation E2

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

Appendix 1: Reasons

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for the endpoints, sub-chronic toxicity (90-day) study (Annex IX, 8.6.2.) and pre-natal developmental toxicity (Annex IX/X, 8.7.2.), adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 2 to 4 in this decision).

0. Grouping of substances and read-across approach

You have sought to adapt the information requirements for a sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.) and pre-natal developmental toxicity study (Annex IX/X, Section 8.7.2.) by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5., there needs to be structural similarity among the substances within a group or category and furthermore, 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 (read-across approach). Furthermore, Annex XI, Section 1.5. lists several additional requirements, including that adequate and reliable documentation of the applied method have to be provided.

You consider to achieve compliance with the REACH information requirements for the registered substance diethyl ether (EC No. 200-467-2) using data of two structurally similar substances: diisopropylether (DIPE) (EC No. 203-560-6) and dimethylether (EC No. 204-065-8) (hereafter the 'source substances').

You have provided read-across documentation in the chemical safety report (IUCLID, Section 13).

You use the following arguments to support the prediction of properties of the registered substance from data for reference substances within the group: "*The registered substance, and the two read-across substances, DME and DIPE, all belong to the class of aliphatic ethers, each possessing two aliphatic alkyl groups connected by a single oxygen atom. Transition from DME to DEE and DIPE occurs with elongation of the aliphatic alkyl groups. DME possesses two methyl (C1) groups, DEE two ethyl (C2) groups and DIPE two isopropyl (C3) groups. These three mono-functional substances are considered to be members of an homologous series of aliphatic ethers, within which in general the properties of the individual homologues are expected to vary in a predictable manner, and in particular, the properties of DEE are expected to lie between those of the smaller DME and the larger DIPE. This expectation is supported by the known physicochemical properties. Considering their structural similarities in sharing a common functional group, and given that their physicochemical properties follow a pattern, DME, DEE and DIPE can be considered as a 'group'*".

You conclude that the source substances are "*appropriate surrogates*" for the registered substance hence they are expected to have a "*similar toxicity profile*".

You propose that the source and registered substances have "*similar*" properties for the above-mentioned information requirements.

ECHA understands that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument is that the similarity in structure and physico-chemical properties between the source and target substances is a sufficient basis for predicting the properties of the substance. These arguments are limited and are in principle not capable of being sufficient. You have not provided any other basis for predicting the properties of the registered substance. Similarity in structure and physico-chemical properties is a prerequisite for applying the grouping and read-across approach. However, ECHA does not accept in general, or in this specific case, that similarity in structure and physico-chemical properties per se is sufficient to enable the prediction of human health properties of a substance, since similarity in structure and physico-chemical properties does not always lead to predictable or similar human health properties, and consequently cannot on its own constitute sufficient evidence of predictable or similar human health properties. Further elements are needed[2], such as a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health properties that does not underestimate risks.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided reasoning why these arguments (i.e. similarity in structure and in physico-chemical properties) added to one another provide sufficient basis for read-across. Secondly, ECHA considers that the arguments when taken all together do not provide a basis for predicting the properties of the registered substance, because the deficiencies in each individual argument are not compensated by the other arguments, and because the arguments taken all together do not provide a reliable basis for predicting the human health properties of the registered substance. Further elements are needed to allow a prediction of human health properties that does not underestimate risks.

In your comments on the draft decision you agree with ECHA that currently the read-across justification does not fulfil the requirements of Annex XI, Section 1.5 of the REACH Regulation. Hence the "*justification for the read-across (...) can be improved*". ECHA understands that you would like to take the update requested by the EU Commission (concerning the extended one-generation reproductive toxicity study) as an "*opportunity to strengthen the read-across approach*" with regards to the sub-chronic (90-day) and developmental toxicity endpoints.

Moreover, in your comments to the proposal for amendment made by a Member State Competent Authority you indicate your intention to update the technical dossier by providing a more robust read across approach including new data on an additional analogue substance. In this update you intend to include the study results for the *in vitro* gene mutation study requested in this decision, and only after this update you will consider whether there would be a need for additional testing with the registered substance. ECHA notes that this decision does not take into account any registration dossier updates after the draft decision has been sent to you [14 December 2016]. Hence the proposed

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals and ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

"two-step process" cannot be considered at this stage.

ECHA points out that all the new information in the later update(s) of the registration dossier, including any new information that may have been generated on analogue substances, will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after ECHA had sent the final decision).

In your comments on the draft decision you also provided the read-across approach, from DME and DIPE to DEE. ECHA notes that the data matrix comparing the physicochemical properties and the toxicological data of the source and target substances seem very relevant for improving the read-across argumentation. However, as regards the physico-chemical properties, ECHA observes that there are differences between the target and source substances, in terms of log Pow values (0.83 for the target, 0.07 for DME and 2.4 for DIPE), water solubility (64.9 g/l for the target, 45.6 g/L for DME and 3.11 for DIPE), and vapour pressure values (71.6 kPa for the target, 513.29 kPa for DME and 19.87 kPa for DIPE). ECHA notes that you have not explained how these differences such as the partition coefficient may affect the predicted hazardous property, how it may impact on the distribution of the substance in the test organism. As regards the "*toxicological comparison of DME, DEE and DIPE*", ECHA does not accept your proposed adaptation argument that the toxicological similarity between the source and target substances is a sufficient basis for predicting the properties of the substance because toxicological similarity is a prerequisite for applying the grouping and read-across approach, but is per se not alone allowing the prediction of human health properties of a substance. This is because toxicological similarity does not always lead to predictable or similar human health properties.

ECHA notes that there are similarities in the data provided for acute toxicity and genetic toxicity in bacteria. However, as regards the higher endpoints (sub-chronic-study, fertility and developmental toxicity) from the data provided the data cannot be compared since for the repeated dose toxicity endpoint there are no oral studies with the the source substances whilst the inhalation studies have different exposure duration. You failed to explain how the data from the short term studies (<90 days) can be used to extrapolate the data to a longer exposure duration and whether it is comparable to the data obtained with the source substances. As regards the fertility endpoint, currently there are no reliable studies for the target and source substances, hence they cannot be compared. Finally, for the developmental toxicity endpoint, as explained in section 3 of this decision, the study provided with the target substance is not reliable and hence it cannot be used to compare data to the studies with the source substances. Moreover, ECHA notes that even though the source and target substances have similar acute toxicity they may have a markedly different reproductive toxicity.

You also claim that from "*specific toxicokinetic studies and general toxicological studies*" the target and source substances are all "*readily absorbed by inhalation, rapidly distribute throughout the body, and are rapidly eliminated once exposure is discontinued*", however there is no comparison data on metabolism ,hence it is not possible to fully compare the toxicokinetics data. You indicate that DIPE can be used as the worst case because this source substance is "*the member of the group with the greatest potential to undergo metabolic transformation in the body*" and it is the "*heavier*" substance hence "*the higher the log Pow is*". The hypothesis that DIPE has more metabolism than the registered substance is not supported by the toxicokinetics data and does not address toxicity which is independent of metabolism. Hence, there is not a reliable basis for considering DIPE as a worst case.

ECHA considers that this grouping and read-across approach does not provide a robust basis whereby the human health effects for the sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.) and pre-natal developmental toxicity study (Annex IX/X, Section 8.7.2.) endpoints may be predicted from data for reference substance(s) within the group. Hence, it does not comply with the general rules of adaptation as set out in Annex XI, 1.5. of the REACH Regulation.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

1. Adequacy for the purpose of classification and labelling and/or risk assessment;
2. Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
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
4. Adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: *S. typhimurium* TA1535; TA1537 or TA97a or TA97; TA98; TA100; *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). This includes four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

You have provided a test (DeFlora, 1981) from the year 1981 according to OECD TG 471 with an assigned reliability score of 2. The test used five different strains of *S. typhimurium* (TA 1535, TA 1537, TA 1538, TA 98 and TA 100). Additionally, you provided another study (Waskell, 1978) from the year 1978 (non-guideline and non-GLP study / reliability 3) that used only two strains of *S. typhimurium* (TA 98 and TA 100). Both studies (DeFlora, 1981; Waskell, 1978) did not include tests with strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). However, since these tests were conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is now required.

Therefore, the provided studies do not meet the current guidelines, nor can they be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

In the technical dossier you have also provided a study (Chen *et al.*, 1993) with the fifth strain *S. typhimurium* [TA102]. However ECHA notes that the study, with an assigned reliability score of 3, does not follow any test guidelines and has not been conducted according to GLP. Furthermore this study (Chen *et al.*, 1993) gave positive results for *S. typhimurium* TA 102. However ECHA notes that the tested substance in this study was an impure form of the registered substance (concentrated aqueous extract from air-exposed diethyl ether), and that the study summary provides no information on the percentage concentration of the impurities used. Finally, the study was performed only without the metabolic activation. Hence, the data provided by this study cannot be considered to be equivalent to the data generated by the corresponding test method since there is no "*adequate and reliable coverage of the key parameters*" as foreseen to be investigated in the corresponding test method. Hence, the conditions for the "*use of existing data*" adaptation, as set out in Annex XI, Section 1.1.2. (2) are not met.

You also provided a bacterial DNA repair study (De Flora *et al.*, 1984) (non-guideline and non-GLP / Rel. 3) with three strains of *E. coli* [WP2, WP67 and CM871] with ambiguous results. However, ECHA notes that this study is not a bacterial reverse mutation test, hence this study record cannot be taken into consideration, as it does not meet the information requirement of Annex VII, Section 8.4.1.

In your comments, you agree that the standard Ames test (including an appropriate 5th strain) is a standard information requirement. However you argue that: "*additional testing is not needed because additional information resulting from the higher Annexes on mutagenicity is available*" and that "for the preparation of the DEE dossier it was not needed to start the examination of the genotoxic properties with studies resulting from Annex VII requirements". ECHA does not agree with these statements because REACH annex X reads (2nd sentence of 2nd paragraph): "Accordingly, the information required in column 1 of this Annex is additional to that required in column 1 of Annexes VII, VIII and IX". ECHA thus considers that in the current (annex X) dossier, the annex VII information requirements should be fulfiled.

You also believe that there are other available mutagenicity studies with "higher significance, the results of the in vitro Mammalian Cell Gene Mutation Assay (Thymidine Kinase Locus/TK +/-) in mouse lymphoma L5178Y Cells (resulting from Annex VIII) is considered sufficient" and you "*do not see the scientific need for an additional study according to OECD TG 471 from a weight-of-evidence perspective*". ECHA confirms that the Ames test, as described in OECD TG 471 (1997), is a standard information requirement according to Annex VII of REACH. ECHA notes that column 2 of annex VII does not provide any adaptation possibility for the data requirement for the Ames test. Regarding your weight of evidence argument, you have not provided an explanation or justification on how the sources of information/studies, which you have provided enable an assumption or conclusion that the registered substance does or does not have a dangerous property with respect to bacterial mutagenicity and 5th strain of Ames test.

In your comments you also refer to the ECHA Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7a: Endpoint specific guidance, Version 5.0, December 2016). You claim that the "*in vitro mammalian cell gene mutation test may be used as an alternative test for this endpoint under certain conditions*". ECHA notes that the Guidance states that the *in vitro* mammalian cell gene mutation test may be used as an alternative test, only "*for substances with significant toxicity to bacteria, not taken up by bacteria, or for which the gene mutation test in bacteria cannot be performed adequately*". This is not the case since there are bacterial studies available with the registered substance.

The *in vitro* mammalian cell gene mutation assay ([redacted], 2010) provided with the registered substance indicates that there is no mutagenicity. However, ECHA notes that the 5th Ames strain may still detect gene mutations which are not being investigated by any of the other four strains. Furthermore, the 5th strains are sensitive to crosslinking agents, oxidative damage, and hydrazines, which the four other strains are insensitive to. In case of positive result with the 5th strain, this would need to be followed up by an *in vivo* gene mutation study. Hence, this "*additional testing*" might still affect the classification and labelling of the substance if there is a positive result with the 5th strain.

Finally ECHA-S notes that no *in vivo* mammalian gene mutation test has been provided in the technical dossier that would potentially provide a justification not to request the 5th Ames strain.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing three study records for a sub-chronic toxicity study (inhalation route) (90-day) (OECD TG 413) with the analogue substances diisopropylethyl ether (EC No. 203-560-6) ([redacted], 1996) and dimethyl ether (EC No. 204-065-8) (Collins *et al.*, 1978; Reuzel *et al.*, 1981). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

In the technical dossier you have also provided, as a key study, an endpoint study record for a sub-chronic toxicity study (90-day) in rats, via the oral route (non-guideline and non-GLP) (EPA, 1987) with the registered substance.

The registered substance is a liquid and has a harmonised classification for Acute toxicity 4 (H302 Harmful if swallowed) and STOT SE 3 (Oral and Inhalation) (H336 May cause drowsiness/dizziness). The vapour pressure of the registered substance is very high (71.6 kPa at 25°C) and the boiling point is 34.65°C. The uses include spraying (PROC 7), which leads to significant exposure to professionals.

In view of the reasons set out above and with reference to the chemical safety report in the dossier the "*inhalation route is the most relevant route for exposure*". Hence the sub-chronic toxicity (90-day) study via the oral route, by EPA (1987), does not fulfill the information requirement of Annex IX, Section 8.6.2. Moreover, the data provided from the oral study (EPA, 1987) is limited as the full details of the original study were not reported in the dossier and are only based on a published summary.

Pursuant to Annex XI, section 1.1.2 referred to above data from human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) shall be considered equivalent if the following conditions are met: (1) adequacy for the purpose of classification and labelling and/or risk assessment, (2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), (3) exposure duration comparable to or longer than the corresponding test method; and (4) adequate and reliable documentation of the study is provided.

ECHA has adopted the standard of a robust study summary as required by Article 10(a)(vii) and defined in Article 3(28) of the REACH Regulation for assessing whether there is adequate and reliable documentation of the sub-chronic toxicity study (90-day), as required by the fourth condition of Annex XI, 1.1.2.

According to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Guidance on the preparation of the robust study summaries is provided in the Practical Guide 3, "How to report robust study summaries", Version 2.0 – November 2012.

The following elements are missing in the submitted sub-chronic toxicity study: study design, detailed description of test conditions, actual dose received by dose level by sex, if known, details on analytical verification of doses or concentrations, toxic response/effects by sex and dose level, provide data preferably in tabular form where applicable, provide additional information that may be needed to adequately assess data for reliability and use including the following if available. Provide at a minimum qualitative descriptions of elements where dose effect related observations were seen: body weight and body weight changes, food/water consumption, description, severity, time of onset and duration of clinical signs (whether reversible or not), sensory activity, grip strength and motor activity assessments (when available), ophthalmologic findings: incidence and severity, haematological findings: incidence and severity, clinical biochemistry findings: incidence and severity, mortality and time to death, gross pathology findings: incidence and severity,

terminal organ weights and organ/body weight ratios, histopathology findings: incidence and severity, statistical treatment of results, where appropriate.

Thus the information about the study (EPA, 1987) fails to meet the requirements of a robust study summary, and accordingly, ECHA considers that there is not adequate and reliable documentation. Hence the study (EPA, 1987) itself cannot be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation since it fails to provide "*adequate and reliable documentation*".

In the technical dossier you have also provided a list of short-term toxicity studies (no guidelines and not conducted according to GLP) with the registered substance, via the inhalation route:
a) Supporting studies: Sub-acute toxicity studies in rats, mice and guinea pigs, inhalation route, with the registered substance. Stevens *et al.* (1975). Rel. 3.
b) Supporting studies: Sub-acute toxicity studies in rats, guinea pigs and rabbits, inhalation route, with the registered substance. Chenoweth *et al.* (1970). Rel 3.

ECHA has assessed whether these non-guideline, non-GLP studies can be relied upon in accordance with the conditions set out in Annex XI, section 1.1.2., summarised above. You consider that these studies are of reliability 3 (not reliable), and so ECHA considers that these studies are not capable of meeting the information requirement. Additionally, these studies do not provide the information required by Annex IX, Section 8.6.2., because of the following:

i. exposure duration is less than 90 days (34 days (Chenoweth *et al.*, 1970) and 35 days (Stevens *et al.*, 1975));
ii. less than 10 males and 10 females per dose group used (8 males and 8 females (Stevens *et al.*, 1975));
iii. less than three concentration levels with the registered substance were used (1 concentration (Chenoweth *et al.*, 1970) and 2 concentrations (Stevens *et al.*, 1975));

The data provided in these studies cannot be considered to be equivalent to the data generated by the corresponding test methods since the studies fail to provide an "*adequate and reliable coverage of the key parameters*" and an "*exposure duration comparable to or longer than the corresponding test method*". Hence, the second and third conditions for the "*use of existing data*" adaptation, according to Annex XI, Section 1.1.2. are not met.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Since the registered substance is a liquid of very high vapour pressure (>10 kPa at at 25°C) and human exposure by the inhalation route is reported in the registration, ECHA considers that the inhalation route is the most appropriate route of administration.

In your comments you claim that "*long term studies with diethylether would be limited to studies by oral application avoiding side effects such as drowsiness and dizziness but also to ensure a safe environment for the test animals and the operators of the studies*". ECHA notes that the "*side effects*" argument is irrelevant since studies are performed to determine whether the substance has toxic effects to the test species, hence these are effects that can be observed and cannot be considered as a reason for not performing the

study via the inhalation route. As regards the "*safe environment*", ECHA notes that in the technical dossier there are short-term repeated dose toxicity studies (Stevens, 1975; Chenoweth, 1970) with the registered substance, in rats, performed via the inhalation route. The maximum dose used in these studies ranges between approximately 25 to 50% of the lower explosive limit (1.85%) of the registered substance, i.e. 0.2-1 % vol. If 25% of the LEL is used, then this dose would be considered as being sufficient. The longer exposure duration of the sub-chronic study (90-day), should not have an effect on the "*safe environment for...the operators of the studies*" and since you failed to provide any evidence from CROs stating the contrary, the study should be conducted via the inhalation route, i.e. the most relevant route of exposure to human, as also indicated in the CSR provided in the technical dossier.

Hence, the test shall be performed by the inhalation route using the test method EU B.29./OECD TG 413.

According to the test method OECD TG 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.
A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a pre-natal developmental toxicity (OECD TG 414) with the analogue substance Diisopropylether (EC no. 203-560-6). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

In the technical dossier you have also provided two study records, as supporting studies, for developmental toxicity in rats and mice, via the inhalation route, with the registered substance. Both studies by Schwetz and Becker (1970) do not follow guidelines, are non-GLP and have been assigned a reliability score of 4 (not assignable). On this basis, ECHA considers that the studies are not capable of providing reliable information. Additionally, these studies do not provide the information required by Annex IX, Section 8.7.2., because the information provided in the studies is based on a published extract which provides very limited information. Important information, such as the number of animals used in the study, the number and amount of doses used, and data on maternal examinations, is missing. Moreover, the maternal exposure duration lasted only for 1 hour; according to OECD TG 414 it should last at least, from implantation to one or two days before expected delivery.

In view of the reasons set above, the data provided in these studies cannot be considered to be equivalent to the data generated by the corresponding test method in accordance with the conditions set out in Annex XI, section 1.1.2. quoted above in section 2 of this decision, since the studies fail to provide an "*adequate and reliable coverage of the key parameters*" and "*adequate and reliable documentation*". Hence, the second and fourth conditions for the "use of existing data" adaptation, according to Annex XI, Section 1.1.2. are not met.

You also provided a publication (only a brief abstract) on a toxicity study in rats via the inhalation route (Garcia-Estrada *et al.* 1990), with the assigned reliability score of 4 (non-guideline and non-GLP). However, this study fails to provide "*adequate and reliable documentation*" since there is no information on the testing parameters, including information on exposure, and the results are missing. Hence the fourth condition for the "*use of existing data*" adaptation, according to Annex XI, Section 1.1.2. is not met.

Furthermore, you have also provided a teratogenicity study in the chick embryos (non-guideline and non-GLP) (Smith *et al.*, 1968). However, this study fails to provide data that can be considered equivalent to the corresponding test method. According to OECD TG 414 "*the preferred rodent species is the rat and the preferred non-rodent species is the rabbit.*" You failed to provide any justification on why a different species has been used, and a test conducted in chicken would not provide data equivalent to testing in mammalian species. Hence, this study record cannot be considered for evaluation of the information requirement of Annex IX, Section 8.7.2.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.
According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.
ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

4. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for

1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation). The technical dossier does not contain information on a pre-natal developmental toxicity study with the registered substance.

In your comments you indicate the intention to update the dossier by "*integrating a "weight of evidence" endpoint in IUCLID section 7.8.2.*" ECHA notes that this decision does not take into account any registration dossier updates after the draft decision has been sent to the Registrant [14 December 2016]. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after ECHA had sent the final decision).
Indeed, ECHA agrees that the decision to conduct the study in a second species depends on the outcome of the first study and all other relevant available data. However, ECHA notes that the decision cannot be postponed to await the results of the pre-natal developmental toxicity study in the first species. The pre-natal developmental toxicity study in the second species is a standard information requirement according to Annex X, section 8.7.2. Hence, since currently there is no study record of a pre-natal developmental toxicity study in the second species in the dossier that would meet the information requirement of Annex X, Section 8.6.7., the request in this compliance check decision is justified.

As explained under section 3 of this decision, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 08 November 2016.

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 took into account your comments and did not amend the request(s).

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

ECHA received proposal for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-54 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2019.

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

3. 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 your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.