EUROPEAN CHEMICALS AGENCY

Helsinki, 27 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114367052-56-01/F
Substance name: Diethyl carbonate
EC number: 203-311-1
CAS number: 105-58-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 20.10.2016
Registered tonnage band: 100-1000T

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]

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), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

3. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD [421/422]) in rats, oral route with the registered substance;**

4. **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;**

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 **3 February 2020**. 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.

[1] No testing for endpoints listed in Annexes IX or X to the REACH Regulation may be started or performed at this moment: A decision only becomes legally effective and binding for you after it has been adopted according to Article 51 of the REACH Regulation. ECHA will take the decision either after the date it has become clear that Member State competent authorities have not made any proposals to amend the draft decision or, where proposals to amend it have been made, after the date the Member State Committee reached a unanimous agreement on the draft decision.

Appeal

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

Authorised[2] by Kevin Pollard, Head of Unit, Evaluation E1

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

Appendix 1: Reasons

TOXICOLOGICAL INFORMATION

In your comments, for the endpoints *in vitro* gene mutation study in bacterial cells (Annex VII, Section 8.4.1.), sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.), screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1.) and pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) you provide adaptation arguments in form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed the scientific and regulatory validity of your Grouping and read-across approach in general.

Grouping and read-across approach for toxicological information

You have sought to adapt the information requirements for endpoints *in vitro* gene mutation study in bacterial cells (Annex VII, Section 8.4.1.), sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.), screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1.) and pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by applying a read-across approach in accordance with Annex XI, Section 1.5. You propose to read-across from dimethyl carbonate (the source substance) to the registered substance.

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 carbonate (EC No. 203-311-1) using data of a structurally similar substance dimethyl carbonate (EC No. 210-478-4) (hereafter the 'source substance').

You have provided a read-across justification in your comments. You use the following arguments to support the prediction of properties of the registered substance from data for reference substance(s) within the group:

- "*For the metabolism of diethyl carbonate a break-down to the constituents carbon dioxide and ethanol is assumed…*" "*Ethanol has a known toxicity profile and is also metabolised without accumulation in the body. If this metabolism takes place the risks associated with it would be limited.*"

- For the source substance "*No studies were specifically designed to investigate the absorption, the distribution, the metabolism and the excretion…*", however, "*According to the toxicity studies, there was no indication of inhalatory or dermal absorption, metabolism, excretion or distribution.*"

- For the source and target substances "*a similar metabolism is assumed*" and "*for their decomposition the generation of one molecule of carbon dioxide and two molecules of ethanol or methanol respectively is assumed.*"

- "*The toxicological concern for diethyl carbonate should…be lower as the decomposition product ethanol is of less concern than the analogue methanol.*"

You propose that the source and registered substances are "*similar*" "*in terms of* (i)

molecular structure (ii) *decomposition* (iii) *bioaccumulation in the body of mammals*" and "*similar metabolism*" and this is your basis for proposing to predict the properties of the registered substance from data on the source substance.

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

ECHA has evaluated the overall rationale for read-across between dimethylcarbonate and the registered substance, and additionally considers endpoint-specific considerations under each of the relevant endpoints.

ECHA's evaluation and conclusion

(i) You propose that the similarity in structure between the source and registered substance is a sufficient basis for predicting the properties of the substance. Under REACH, any read-across approach must be based on structural similarity between the source and registered substances. However, structural similarity alone is not sufficient to justify the possibility to predict property(ies) of the target substance by read-across. This is because similarity in structure does not always lead to predictable or similar human health properties, and hence predictions based solely on structural similarity are not a reliable basis for predicting human health properties. The read-across hypothesis must establish why a prediction for a toxicological property is possible and should be based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and target substances. The possibility for predictions of similar properties should be linked to the common structural aspects. The differences in the chemical structures should not influence the toxicological properties or do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. In the present case, further elements are needed[3], 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.

(ii) You also propose that the target substance may be metabolised into ethanol and carbon dioxide. "*Carbon dioxide is a natural metabolite in the human body*" while "*ethanol has a known toxicity profile*" hence it can be used to predict the properties of the registered substance. However, you have not provided data to show that the registered substance degrades rapidly into metabolites, such that there is no significant exposure to the registered substance. In the absence of such a demonstration, ECHA considers that the properties of the metabolites do not provide a reliable basis for predicting the properties of the parent substance.

(iii) Your hypothesis is also based on similar bioaccumulation. According to the technical dossier the bioaccumulation potential for the registered substance is considered as being low based on study results. For the source substance you state that there are "*no studies...to investigate the bioaccumulation*"; however, it is also considered as having a low bioaccumulation potential based on the log Kow value (<3). Bioaccumulation relates to the ability of a chemical to accumulate in the body, and this property does not have any relationship to the intrinsic toxicity of the substance. For example, there are substances with very low accumulation potential which are high potency toxins, and chemicals with high accumulation potential which have low toxicity. Therefore, ECHA considers that this property alone cannot provide a reliable basis for predicting the

[3] 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).

human health properties of the target substance.

(iv) In your comments you also assume a "*similar metabolism*" for both the source and target substance. This assumption is based on the "*no indication of inhalatory or dermal absorption, metabolism, excretion or distribution*" from toxicity studies of the source substance. However, since no toxicokinetics data are available for the source substance or target substance, ECHA considers that the assumption of similar metabolism is not adequately justified. Moreover, similar metabolism of two substances does not address whether there are differences in the toxicological properties of the parent substance. Therefore this assumption of similar metabolism is not a reliable basis for predicting the human health properties of the registered substance.

Additionally, ECHA has taken into account all of your arguments (i.e. structural similarity, the properties of the main metabolite, bioaccumulation, metabolism) together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, ECHA considers that the current arguments provided in your comments when taken all together do not provide a sufficient basis for predicting the properties of the registered substance, because the individual arguments do not complement each other. The read-across justification fails to establish why a prediction for a toxicological property is possible, based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and target substances. Thus the conditions of Annex XI, 1.5 are not met, and the proposed adaptation cannot be accepted.

Based on the above, ECHA considers that this grouping and read-across approach does not provide a robust basis whereby the human health effects may be predicted from data for reference substance(s) within the group, and hence does not comply with the general rules of adaptation as set out in Annex XI, Section 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 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "In vitro gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

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 from the year 1986 according to OECD TG 471 with an assigned reliability score of 2. The test used four different strains of S. typhimurium TA TA1535, TA1537, TA98, TA100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, since the test was 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 study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.
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.

In your comments to the draft decision sent to you under Article 50 REACH (the "initial draft decision") you additionally indicate your intention to adapt this information requirement by providing the *in vitro* gene mutation study in bacteria with the analogue substance dimethyl carbonate. The study provided in the comments (according to Guidelines for Screening Mutagenicity Testing Of Chemicals (Japan) / Rel. 1 / GLP compliant) is compliant. However, as explained above, under the *Grouping and read-across approach for toxicological information* section, since the read-across approach cannot be accepted, the study provided in the comments cannot be used to fulfil the information requirement of Annex VII, Section 8.4.1 for the registered substance.

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 the 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), oral 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 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX 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 standard infromation requirement in two ways.

First, ECHA understands that you to have sought to adapt this information requirement according to Annex IX, Section 8.6.2., column 2, 2nd sub-paragraph, whereby "the sub-chronic toxicity study (90 days) does not need to be conducted if: a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used." However, ECHA has evaluated all the studies in the dossier and considers the data on long-term chronic toxicity is not reliable for the reasons set out below and hence there is no reliable chronic toxicity study available. Hence, the criteria according to Section 8.6.2., column 2 or Annex XI, Section 1.1.2. (2) are not met. You have also provided other studies which do not meet the information requirement, and these are discussed below.

In the technical dossier you have provided the following study records which are relevant for Repeated dose toxicity, and ECHA sets out its considerations for each study below.

Study oral.001. This is a non-guideline oral drinking water mouse key study of 83 weeks (Brown, 1978) of reliability 2 with unspecified GLP status. ECHA has evaluated this study in light of Annex XI, 1.1.2. Key parameters of OECD TG 408 such as ophthalmological examinations and clinical biochemistry were not investigated. In addition, there is no information justifying the dose of substance (see paras. 21-25 of OECD TG 451), and the top dose does not appear to be chosen to elicit evidence of toxicity, as required by paragraph 22 of OECD TG 451. Animals were weighed monthly until week 25, and then every three months, whereas TG 451 requires weekly measurements for the first 13 weeks and then at least monthly thereafter. The exposure duration of an OECD 451 study should be 24 months, unless there is specific justification (Para 31, 32 of OECD 451). The provided study is 18 months long and there is no justification for the deviation. ECHA considers there is not adequate and reliable coverage of key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3). Pursuant 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: the tissues investigated at gross necropsy and histopathological examination are not listed, nor a listing of histopathological results; rationale for dose level selection; test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation; mortality and time to death (indicate number died per sex per dose and time to death); body weight gain; organ weights; clinical chemistry; haematology; necropsy findings: nature and severity;

histopathological findings: nature and severity (neoplastic and non-neoplastic); time to tumours and statistical results. Consequently, ECHA considers that there is not adequate and reliable documentation of the study.

Study oral.002. This is a non-guideline oral drinking water rat supporting study of 100 weeks (Bornmann and Loeser 1966) of reliability 2 with unspecified GLP status. ECHA has evaluated this study in light of Annex XI, 1.1.2. Key parameters of OECD TG 408 such as ophthalmological examinations and clinical biochemistry were not investigated. In addition, there is no information justifying the dose of substance (see paras. 21-25 of OECD TG 451), and the top dose does not appear to be chosen to elicit evidence of toxicity, as required by paragraph 22 of OECD TG 451.
ECHA considers there is not adequate and reliable coverage of key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3). Pursuant 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: the tissues investigated at gross necropsy and histopathological examination are not listed, nor a listing of histopathological results; rationale for dose level selection; test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation; mortality and time to death (indicate number died per sex per dose and time to death); body weight gain; organ weights; clinical chemistry; haematology; necropsy findings: nature and severity; histopathological findings: nature and severity (neoplastic and non-neoplastic); time to tumours and statistical results. Consequently, ECHA considers that there is not adequate and reliable documentation of the study.

ECHA additionally notes that this endpoint study record includes results of a dog study. ECHA notes that the study has the same shortcomings as pointed out for the rat study (see above), but also that the study has insufficient animal numbers (1 male and two female per dose group), a varying dosing schedule (twice a week, then four times a week), only one treated dose group, and the treatment was for 10 weeks. ECHA has evaluated this study in light of Annex XI, 1.1.2. ECHA considers that there is not adequate and reliable coverage of key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3), and additionally, there is not exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter.

Study oral.003. This refers to a review of study "oral.001", Brown 1978. The deficiencies set out for 'Study oral.001' (above) are relevant for this study record.

Study oral.004. This is a non-GLP, non-guideline 40-week study in mice (Berenblum, 1959), which is considered to be of reliability 3 (not reliable), and you state "Description of the method often not very clear. The experimental results are doubtful, because the mortality rate in the control group was rather high." Since you have considered this study to be not reliable, ECHA has not further evaluated this study.

Study inhalation.001. This is a non-GLP, non-guideline 4-week key study ([redacted] 1970) using mice, rats and rabbits, of reliability 2. ECHA has evaluated this study in light of Annex XI, 1.1.2. ECHA considers there is not exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter (4 weeks, versus 90-days). There is only one dose group in Trial 4 (three

required in OECD 408), there is no justification for dose setting, and the dosing does not comply with para 13 of OECD 408, "the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering." ECHA considers that there is not adequate and reliable coverage of key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3).

Study dermal.001. This is a non-GLP, non-guideline mouse key tumour initiation study of reliability 3 (Roe and Salaman, 1955; Salaman and Roe, 1956). You state "No information was given concerning the gender of the animals. The description of the conducted methods was not layed out in detail in Salaman 1956, but were only referred to in another publication (Roe 1955)." Since you have considered this study to be not reliable, ECHA has not further evaluated this study.

Study carcinogenicity.001. This is a non-guideline study from a database with unspecified-GLP status, which has reliability 4 (not assignable) and is assigned as part of a weight of evidence. You state "only two one-sentence statements without background data; data from HSDB database". Since you have considered this study to be not assignable for reliability, ECHA has not further evaluated this study.

Study carcinogenicity.002. This is the same study as "oral.004", with reliability 3 (not reliable), and is assigned as part of a Weight of Evidence. ECHA considers this study inadequate for the same reasons as set out above for "oral.004".

Study carcinogenicity.003. This is a non-GLP, non-Guideline study of reliability 3 (not reliable), referring to the same studies as "dermal.001" and is assigned as part of a Weight of Evidence. ECHA considers this study inadequate for the same reasons as set out above for "dermal.001".

Study carcinogenicity.004. This is the same study as "oral.001" . It is listed as a key study. ECHA considers this study inadequate for the same reasons as set out above for "oral.001".

You have assigned carcinogenicity studies 001, 002 and 003 as part of a Weight of Evidence, but you have not provided any documentation of the reasoning of your Weight of Evidence. ECHA notes that you consider two of these studies as being not reliable, and the remaining study as being not assignable in view of the paucity of information about the study. You have not provided a reasoning as to why these studies provide a sufficient weight of evidence, and ECHA considers that there is not sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property (i.e. to satisfy the requirements of Annex IX, 8.6.2), while the information from each single source alone is regarded insufficient to support this notion.

Therefore, this adaptation of the information requirement cannot be accepted.

Second, in your comments on the initial draft decision you indicate your intention to adapt this information requirement by providing the sub-chronic toxicity study (90-day) with the source substance dimethyl carbonate. The study provided in the comments (according to OECD TG 408 / Rel. 1 / GLP compliant) satisfies the requirements for a 90-day study. However, as explained above, under the *Grouping and read-across approach for toxicological information* section, since the read-across approach cannot be accepted, the study provided in the comments cannot be used to fulfil the information requirement of Annex IX, Section 8.6.2. for the registered substance.

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. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. The registered substance has a low vapour pressure of 1440 Pa. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route may occur (industrial spray applications) there is no indication for a significant skin and eye irritation potential. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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: Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from in vitro methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

For the toxicity to reproduction endpoint you are seeking to adapt this information requirement in two ways.

First, you seek to adapt this information requirement in accordance with Annex XI, Section 1.1.2., by providing a key study record: Multigeneration study on rats, via the oral route (Bornmann & Loeser, 1966) with the registered substance (No guideline followed. Not conducted according to GLP. Reliability 2.). Pursuant 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. ECHA notes that very few of the elements listed under "5.5 Toxicity to Reproduction/Fertility" are provided, to the extent that the experimental design and the measured parameters are not clear. Hence you have not provided adequate and reliable documentation. In addition, it seems from this information that mating is only performed with two groups (control and 0.015% test substance). If that is the case, ECHA considers that there is not adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), since OECD Test Guidelines 421/422 require three test groups, and the highest dose level should be chosen with the aim of inducing toxic effects but not death nor obvious suffering.

You have also provided a key study by Kimmerle (1970) 4 weeks inhalation study, repeated dose toxicity (7 hours at 5 subsequent days for 4 weeks). ECHA has assessed this study according to Annex XI, Section 1.1.2, and considers that while this can provide information on the gonads, it does not cover several of the key parameters which measure reproductive performance and offspring viability in a screening study. Moreover, the study used only a single dose group. ECHA considers that there is not adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

Therefore the adaptation of the information requirement cannot be accepted. Hence the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement.

Second, in your comments on the initial draft decision you indicate your intention to adapt this information requirement by using the pre-natal developmental toxicity study with the analogue substance dimethyl carbonate. ECHA notes that an existing prenatal developmental toxicity study is an appropriate basis to adapt the requirement for a reproductive toxicity screening study according to Annex VIII, Section 8.7.1., column 2. However, as explained above, under the *Grouping and read-across approach for toxicological information* section, since the read-across approach cannot be accepted, the study provided in the comments cannot be used to fulfil the information requirement of Annex VIII, Section 8.7.1. for the registered substance.

Consequently there is an information gap and it is necessary to provide information for this endpoint.

The substance is a liquid with relatively low vapour pressure (1440 Pa). The substance is not eye or skin irritant. Although there are industrial spraying applications, 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 6.0, July 2017) 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.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

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:

Reproductive/developmental toxicity screening test (test method: OECD TG 421) or Combined repeated dose toxicity study with the reproduction/developmental toxicity

screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7a, section R.7.5 and 7.6 (version 5.0, December 2016). You should also carefully consider the order of testing especially the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure unnecessary animal testing is avoided, paying particular attention to ECHA's end point specific guidance document[4].

4. 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 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX 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 are seeking to adapt this information requirement in two ways.

First, you have provided three study records, none of which is conducted according to GLP or to a test guideline. ECHA has evaluated these studies according to Annex XI, 1.1.2.

In the technical dossier you have provided a non-GLP, non-guideline key study record for the maternal, embryotoxicity and teratogenic effects on rats, via the oral route, with the registered substance ([redacted], 1969) of reliability 2. The number of pregnant females used per dose group is less than 20, as specified in OECD TG 414 para. 10, (only 10 females per dose group). Para 12 of OECD 414 specifies that the substance should be administered daily from implantation (e.g., day 5 post mating) to the day prior to scheduled caesarean section, whereas this study reports dosing from day 6 to 15 of gestation, and so the key parameter of exposure for all relevant developmental stages is missing. Para 13 of OECD 414 provides that "Unless limited by the physical/chemical nature or biological properties of the test substance, the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering." There is evidence that this requirement has not been met, since the animals are without any negative effects.

For these reasons, this study provides inadequate and unreliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3).

You have provided a non-GLP, non-guideline 3-generation reproductive toxicity as a key study (Bornmann and Loeser, 1966). Pursuant 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

[4] ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance Version 5.0, December 2016, p 461-2 (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf).

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. ECHA notes that very few of the elements listed under "5.6 Developmental toxicity/ teratogenicity" are provided, to the extent that the experimental design and the measured parameters are not clear. Hence you have not provided adequate and reliable documentation.

You have provided a non-GLP, non-guideline study with hamsters (DiPaolo, 1967), which you assign reliability 2, but you state "disregarded due to major methodological deficiencies". ECHA has assessed this study according to Annex XI, 1.1.2. The study used only 3 animals per dose (20 in the guideline), doses once by i.p at day 8 ("from implantation (e.g., day 5 post mating) to the day prior to scheduled caesarean section" in the guideline), kills on day 13 ("Females should be killed one day prior to the expected day of delivery" in the guideline, 16 day gestation for a golden hamster). Accordingly, ECHA considers that there is not adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

Second, in your comments on the initial draft decision you indicate your intention to adapt this information requirement by providing the pre-natal developmental toxicity study with the analogue substance dimethyl carbonate. The study provided in your comments follows the OECD TG 414 and complies with GLP. However, as explained above, under the *Grouping and read-across approach for toxicological information* section, since the read-across approach cannot be accepted, the study provided in the comments cannot be used to fulfil the information requirement of Annex IX, Section 8.7.2. for the registered substance.

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 6.0, July 2017) 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 (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.

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 16 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 requests.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

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

3. 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.