ECHA
EUROPEAN CHEMICALS AGENCY

[If applicable: MSC identifiers]

Helsinki, 13 December 2018

Addressee [redacted]

Decision number: TPE-D-2114453723-48-01/F
Substance name: ethyl methyl carbonate
EC number: 433-480-9
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/12/ 2017
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (OECD TG 408) using the using the analogue substance dimethyl carbonate is rejected, you are requested to perform:

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

While your originally proposed test for Pre-natal developmental toxicity study (414) using the analogue substance dimethyl carbonate is rejected, you are requested to perform:

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**

You are additionally requested to perform:

3. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbits or rats), oral route using 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 an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***21 December 2020***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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

The decision of ECHA is based on the examination of the testing proposals submitted by you and scientific information submitted by third parties.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408 with the analogue substance dimethyl carbonate (EC No 203-311-1).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance dimethyl carbonate (EC No 203-311-1).

Your proposed adaptation argument is that *"the 2 substances share the similar formula structure. The difference caused due to the length of carbon chain will be very little".* Structural similarity is a prerequisite for applying the grouping and read-across approach. However structural similarity does not necessarily lead to predictable or similar human health properties. You have not established why a prediction for a human health property is reliable. Thus structural similarity per se is not sufficient to enable the prediction of human health properties of a substance.

On that basis, the requirement of Annex XI, Section 1.5., that human health effects may be predicted from data for reference substance(s) within the group, has not been met.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, the registered substance is a liquid with a low vapour pressure and no likelihood of inhalation exposure based on the use information. ECHA agrees 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. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Therefore, ECHA considers that a study performed by the oral route with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You proposed testing in rats. According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has indicated that "*the published Registration Dossier contains a 28-day rat oral toxicity study performed with the substance and a 2-year rat drinking water study with the close structural analogue diethylcarbonate. The 2-year study is assessed as Klimisch 2; the data therefore appear to be adequate to meet the Annex X data requirements for repeated dose toxicity. Furthermore, the 28-day study with the registered substances reports a NOAEL of 1000 mg/kg bw/d. The substance is not classified for human health endpoints and therefore meets the definition of a low (sub)acute toxicity profile? according to Taylor et al (2014), Taylor & Andrew (2017). Given the low toxicity of the substance and the availability of a chronic toxicity study, the value of the proposed 90-day study is therefore questioned. Taylor K et al (2014). The added value of the 90-day repeated dose oral toxicity test for industrial chemicals with a low (sub)acute toxicity profile in a high quality dataset. Regul Toxicol Pharmacol. 69(3):320-332. Taylor K & Andrew DJ (2017). The added value of the 90-day repeated dose oral toxicity test for industrial chemicals with a low (sub)acute toxicity profile in a high quality dataset: An update. Regul Toxicol Pharmacol. 90:258-261.*"

ECHA acknowledges that the third party has proposed a read across approach for you to consider. ECHA notes that it is your responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Section 1.5. Therefore, you may assess whether you can justify a read-across as suggested by the third party. If the information requirement can be met by way of adaptation, you may include the adaptation argument with all necessary documentation according to Annex XI, Section 1.5 in an updated registration.

ECHA further stresses that the third party has referred to information disseminated on ECHA's website from the lead registrant's dossier for the registered substance. The 28-day study conducted with the registered substance and the 2-year study performed with the analogue substance diethylcarbonate are not currently included in your registration dossier. You have opted out from the joint submission for the information requirement of Annex IX, Section 8.6.2 and proposed to conduct a sub-chronic (90-day) toxicity study with the analogue substance dimethyl carbonate (EC No 203-311-1). ECHA has examined this testing proposal, as detailed in Appendix 1, Section 1.a above.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Sub-

chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408) while your originally proposed test for Sub-chronic toxicity study (90-day) in rats, by the oral route with the analogue substance dimethyl carbonate (EC No 203-311-1) is rejected according to Article 40(3)(d) of the REACH Regulation.

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

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to OECD TG 414 by the oral route with the analogue substance dimethyl carbonate (EC No 203-311-1).

Your proposed adaptation argument is that *"the 2 substances share the similar formula structure. The difference caused due to the length of carbon chain will be very little*. Structural similarity is a prerequisite for applying the grouping and read-across approach. However structural similarity does not necessarily lead to predictable or similar human health properties. You have not established why a prediction for a human health property is reliable. Thus structural similarity per se is not sufficient to enable the prediction of human health properties of a substance.

On that basis, the requirement of Annex XI, Section 1.5., that human health effects may be predicted from data for reference substance(s) within the group, has not been met.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.
ECHA considers that a study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rat as a first species. According to the test method 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 the rat or rabbit as a first species.
ECHA agrees 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) Chapter R.7a, Section 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 due to the low vapour pressure and no inhalation exposure.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-

natal developmental toxicity study in a first species (rats or rabbit), oral route (test method: OECD TG 414) while your originally proposed test for pre-natal developmental toxicity study in rats according to OECD TG 414 by the oral route with the analogue substance dimethyl carbonate (EC No 203-311-1) is rejected according to Article 40(3)(d) of the REACH Regulation.

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

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for 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).

As outlined above under 2. ECHA has requested testing for a pre-natal developmental toxicity study in a first species according to OECD TG 414. ECHA notes that you registered your substance for 1000 tonnes or more per year and that your technical dossier does not contain information on a pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.). Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method 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 in a second species (rabbit or rats), 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 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, with a low vapour pressure and lack of inhalation exposure based on the use information, ECHA concludes that testing should be performed by the oral route. Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit or rat), oral route (test method: OECD TG 414).

Notes for your consideration

Before performing a pre-natal developmental toxicity study in a second species you should consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species or any other new information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement and underlying scientific justification.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 29 December 2017.

ECHA held a third party consultation for the testing proposals from 28 February 2018 until 16 April 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **3 September 2018**, 30 calendar days after the end of the commenting period.

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 did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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 decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, 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.