Helsinki, 25 June 2019

Addressee: [redacted]

Decision number: TPE-D-2114470973-38-01/F
Substance name: Dimethoxymethane
EC number: 203-714-2
CAS number: 109-87-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 10/12/2018
Registered tonnage band: [redacted]

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.

Your initial testing proposal is accepted and you are requested to carry out:

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance having 99.5 – 100% (w/w) degree of purity, specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

You have to submit the requested information in an updated registration dossier by **2 July 2021**. You also have to update the chemical safety report, where relevant.

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 **Claudio Carlon,** Head of Unit, Hazard Assessment

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

Appendix 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. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X of the REACH Regulation. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 an extended one-generation reproductive toxicity study according to OECD TG 443 by the oral route with the following justification and specification of the study design: Based on the relevant existing data, there are no triggers for inclusion of extension of Cohort 1B to include the F2 generation, developmental neurotoxicity Cohorts 2A and 2B, or developmental immunotoxicity Cohort 3. Hence, basic test design with ten weeks premating exposure duration for parental (P0) animals is proposed.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that the proposed study design is appropriate to fulfil the information requirement of Annex X, Section 8.7.3. 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. Thus, an extended one-generation reproductive toxicity study according to column 1 of 8.7.3., Annex X is required. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed ten weeks premating exposure duration for the parental (P0) generation.

To ensure that the study design adequately addresses the fertility endpoint, the duration of

the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of Section 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed not to include an extension of Cohort 1B with the following justification: "*Based on the existing toxicological data, there are no trigger for inclusion of extension of Cohort 1B to include the F2 generation*".

ECHA agrees that the criteria to extend the Cohort 1B are not met and concludes that Cohort 1B must not be extended to include mating of the animals and production of the F2 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of Section 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You proposed not to include Cohorts 2A and 2B with the following justification: "*Based on the existing toxicological data, there are no trigger for inclusion of developmental neurotoxicity Cohorts 2A and 2B*".

ECHA agrees that the criteria to include Cohorts 2A and 2B are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of Section 8.7.3., Annex X.

You proposed not to include Cohort 3 with the following justification: "*Based on the existing toxicological data, there are no trigger for inclusion of developmental immunotoxicity Cohort 3*".

ECHA agrees that the criteria to include Cohort 3 are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

Species and route selection

You proposed testing in rats.

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

You proposed testing by the oral route. 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.

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.

The third party provided their considerations of the study design and stated that "*The* basic study design (Cohorts 1A and 1B without extension) *is considered to be appropriate in the absence of any triggers or conditions necessitating the inclusion of additional cohorts or a further generation*". However, the third party did not provide any scientific data which would fulfil this information requirement.

In your comments on the draft decision and in your updated technical dossier, with submission number [redacted], you have informed ECHA that instead of performing the proposed extended one-generation reproductive toxicity study you intend to fulfill this standard information requirement by using the data on reproductive / development toxicity screening studies (OECD TG 421) with the analogue substances, Ethylal (EC no. 207-330-6) and Butylal (EC no. 219-909-0). You also provided a read-across justification in the updated dossier.

However, ECHA notes that the reproduction/developmental toxicity screening test (OECD TG 421) does not provide the information required by Annex X, section 8.7.3., because many key elements are missing or limited in the OECD TG 421 study. For example the exposure does not cover spermatogenesis and folliculogenesis, extensive postnatal investigations of the fully exposed F1 generation up to the adulthood are not included and the lower statistical power does not allow similar sensitivity of investigations. Therefore, the OECD TG 421 study cannot be used to fulfil the information requirement.

Moreover, ECHA notes that there is no extended one-generation reproductive toxicity study available with any of the proposed analogue substances (Ethylal and/or Butylal). Therefore, there is no data with the analogue substances that can be used to predict the data for the

registered substance for this particular endpoint. Hence, for this endpoint your adaptation according to Annex XI, Section 1.5. cannot be accepted.

In your comments you also refer to the OECD TG 414 studies with the registered and the analogue substances. ECHA notes that the OECD TG 414 study mainly provides information on prenatal developmental toxicity; therefore it cannot be used to to fulfil the information requirement.

Finally, you also indicated that if the read-across to the analogue substances is not accepted by ECHA, a testing proposal will be submitted for an OECD TG 421 study with the registered substance to confirm the prediction of the read-across. ECHA notes that OECD TG 421 is a standard information requirement at Annex VIII, therefore you may decide to perform the study without submitting a testing proposal. However, according to Annex VIII, Section 8.7.1, column 2, you do not need to conduct a screening for reproductive/developmental toxicity study (OECD TG 421/422) given that a pre-natal developmental toxicity study in rats with the registered substance is available in the technical dossier.

c) Outcome

ECHA notes that the registration dossier covers two different compositions, one being "Dimethoxymethane" having 99.5 – 100% (w/w) degree of purity, and the other "Dimethoxymethane technical grade" having 93 - < 100% (w/w) degree of purity. The latter can have a higher concentration of impurities, like methanol and formaldehyde, with known health hazard classifications. Furthermore, you have classified the technical grade composition for health hazards Acute Tox 4 and STOT SE2 (optic nerve, central nervous system) whereas you have not classified the higher purity composition for any health hazards. To avoid any confounding effects potentially caused by the impurities with known health hazard classifications the the registered substance with 99.5 – 100% (w/w) degree of purity should be tested.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the initially proposed study with the registered substance having 99.5 – 100% (w/w) degree of purity subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by

including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

Deadline to submit the requested Information

In the initial draft decision communicated to you, the deadline to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the deadline to 36 months. To justify this request you state that you need more time to obtain information on the analogue substances. However, as indicated above, your adaptation according to Annex XI, Section 1.5. cannot be accepted. Therefore, ECHA has not modified the deadline of the decision.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 15 January 2018.

ECHA held a third party consultation for the testing proposals from 26 March 2018 until 11 May 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **10 December 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 took into account your comments, did not amend the request and did not amend the deadline.

You updated your registration on 10 December 2018. ECHA took the information in the updated registration into account, and did not amend the draft decision. The updated information is reflected in the Reasons (Appendix 1).

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 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 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.