ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114343381-57-01/F Helsinki, 21 September 2016

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For dimethoxymethane, CAS No 109-87-5 (EC No 203-714-2), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for dimethoxymethane, CAS No 109-87-5 (EC No 203-714-2), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of [redacted] per year. This decision does not take into account any updates submitted after 21 July 2016, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage. ECHA notes, in particular, that the information requirement of Annex IX/ X, Section 8.7.3 has not been addressed in this decision.

The compliance check was initiated on 28 November 2013.

On 28 November 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 45 days of the receipt of the draft decision. (deadline exceptionally granted due to the commenting period falling on the Christmas and New Year period). That draft decision was based on submission number [redacted].

On 15 January 2015 ECHA received comments from the Registrant on the draft decision.

On 15 January 2015 the Registrant updated his registration dossier with the submission number [redacted]. On 24 July 2015, the Registrant again updated his registration dossier with the submission number [redacted].

The ECHA Secretariat considered the Registrant's comments and update.
On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 21 July 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vi) and/or (vii), 12(1)(e), 13 and Annexes VII, IX and X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD 414) in rabbits, oral route;

Note for consideration by the Registrant:

The Registrant 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 of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

B. Deadline for submitting the required information

Pursuant to Articles 41(4) and 22(2) of the REACH Regulation the Registrant shall submit to ECHA by **28 September 2017** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 18 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a growth inhibition study on aquatic plants (Annex VII, Section 9.1.2), a boiling study (Annex VII, Section 7.3), a relative density study (Annex VII, Section 7.3), and a viscosity study (Annex IX, Sectio 7.17). As these studies are not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of [redacted] per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.)

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for a substance registered for [redacted] 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 contains information on a pre-natal developmental toxicity study in rats by the inhalation route using the registered substance as test material. However, there is no information available for a pre-natal developmental toxicity study in a second species.

As explained above, the information available 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.

In his comments to the draft decision as well as the updated dossier, the Registrant included information derived from the application of (Q)SAR approaches to predict developmental toxicity in the second species. The information included in the comments as well as the updated dossier dossier was for developmental toxicity on rabbit, rat, rodent and mouse using the Leadscope Developmental toxicity Suite. The Registrant provided this information to show "the absence of significance in sensitivity of species tested".

ECHA has analysed the information in the Registrant's comments as well as the updated dossier. This analysis is presented below.

The quality and reliability of the (Q)SAR models can be assessed in the light of the criteria established in Section 1.3. of Annex XI to the REACH Regulation:

- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided.

Adequate and reliable documentation should provide information on the scientific validity of the approach. The justification for using the (Q)SAR information should be based on the use of the QSAR Reporting Formats described in ECHA Guidance on information requirements and chemical safety assessment (May 2008), Chapter R.6 (Section R.6.1.6.).
First, ECHA notes that the ECHA Guidance states the following on the use of (Q)SAR models for reproductive toxicity:

"There are a large number of potential targets/mechanisms associated with reproductive toxicity which, on the basis of current knowledge, cannot normally be adequately covered by a battery of QSAR models. In principle QSAR models are potential adaptation possibilities according to REACH Annex XI, 1.3, but they should adequately cover the endpoint in question – all the key aspects/parameters should be covered."

And

"A particular challenge for this endpoint is the complexity and amount of information needed from various functions and parameters to evaluate the effects on reproduction. Not all necessary aspects can be covered by a QSAR prediction. Therefore, a negative result from current QSAR models predicting that the substance has not a particular property, cannot be interpreted as demonstrating the absence of a reproductive hazard unless there is other supporting evidence. Another limitation of QSAR modelling is that dose response information, for example the N(L)OAEL, required for risk assessment is not provided."

ECHA notes that the QSAR adaptation put forward by the Registrant suffers from the same deficiency as highlighted in the Guidance quoted above. Specifically, the model provides a prediction of the probability that the substance is non-toxic or toxic. As such, the output of this prediction does not provide any dose-response information, and cannot be used to obtain a N(L)OAEL value. Therefore, the adaptation does not meet the criteria set out in Annex XI, 1.3, on the use of (Q)SARs. Specifically, the information does not meet the requirement that: the results are adequate for the purpose of classification and labelling and/or risk assessment.

In addition to the above, ECHA assessed the provided Leadscope models and predictions to the extent possible. For all four endpoints it is found in the QPRFs that the closest analogues are not sufficiently similar to consider the predictions as reliable. In the case of mouse toxicity, even if one analogue were deemed to be similar enough (diethyl ether), this analogue is denoted POSITIVE in the training set (i.e. based on experimental result). Diethyl ether is found POSITIVE also in the rat model training set. In addition another analogue, triethylene glycol dimethyl ether, is also POSITIVE in mouse. The latter substance was found as NEGATIVE in the rabbit model but uncertainty is still high bearing in mind this high level of aggregation of the endpoint result (in POS/NEG scale). The overall predictivity of the models is around 70-75% and the large number of descriptors used (even at the limit of acceptable ratio between descriptors and compounds in the training set) does not support reliable prediction. ECHA also considers that the general rodent model is not suitable for data gap filling due to aggregation of the species responses in that model. As a result of the above considerations, ECHA considers that results are derived from a (Q)SAR model whose scientific validity has not been established, and this is an additional reason that the requirements of Annex XI, 1.3 are not met.

Thus, based on the arguments above, ECHA considers that the requirements of Annex XI, 1.3, have not been met, that there is consequently a data gap, and that testing in a second species (rabbit) is necessary.

In addition to the proposed (Q)SAR adaptation, the Registrant indicated that if the adaptation is not accepted and a pre-natal developmental toxicity study is needed on a second species (rabbit), that this study should be performed via the oral route, rather than the inhalation route. The Registrant stated that it is not possible to perform the study via nose only exposure in the rabbit, and that there is limited experience in CROs in performing inhalation studies with rabbits, and no experience performing pre-natal developmental toxicity studies via inhalation in the rabbit. The Registrant further indicated that the absence of such experience, and the lack of availablility of historical data may complicate the

interpretation of the study. Furthermore, the Registrant indicated that based on the avialable information, there is no reason to expect any route specific toxicity for this substance.

ECHA has considered the Registrant's comments regarding the route of exposure. First, ECHA notes that the default route of exposure for the PNDT study is the oral route, except for gases, where the inhalation route is the default route of exposure. For substances that are gases that are registered at [redacted] tpa, it will be necessary to perform a PNDT study via the inhalation route in the rabbit.

ECHA notes that while performing a PNDT study via nose only exposure in rabbits may be challenging, it is nevertheless possible to perform the study via full body exposure. Indeed, there are examples of such studies available. In addition, ECHA notes that while performing the study via nose only exposure in rabbits may be more stressful compared to oral exposure, a PNDT study done via full body exposure may be *less* stressful to pregnant rabbits compared to gavage dosing. Therefore, ECHA disagrees with the Registrant's comment that inhalation exposure is not in line with animal welfare legislation or is scientifically not justified in all cases. While performing such a study may be more challenging and more costly, ECHA considers that in some cases it is possible and necessary to perform a PNDT study on rabbits via the inhalation route. Indeed ECHA has previously consulted CROs on the possibility of performing such studies and has been informed that such studies are feasible.

This registered substance subject to the present decision is a liquid at room temperature, however, it has a high volatility as evidenced by the vapour pressure and the low boiling point of the substance. Based on this, ECHA considered that the test should be performed by the inhalation route in the draft decision sent to the Registrant.

Based on the physico-chemical properties of the substance, it is technically possible to perform this study via either the inhalation route or the oral route. ECHA considers that each route of exposure for this particular study offers some advantages and disadvantages. While ECHA disagrees with the Registrant's comments regarding the feasibility of performing the study via the inhalation route, as well as his comments on animal welfare aspects of performing the study, ECHA agrees that in this particular case there is no toxicological information for this substance that would favor performing the study via the inhalation route over the oral route. ECHA therefore concludes that a study performed via the oral route would be sufficient to address the data gap for this particular endpoint.

The test in the first species was carried out by testing a rodent species and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species and the test substance is usually administered orally.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 414) in rabbits by the oral route.

IV. Adequate identification of the composition of the tested material

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given 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 substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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.