ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 15 November 2019

Addressee: [redacted]

Decision number: CCH-D-2114488830-40-01/F
Substance name: Methylamine
EC number: 200-820-0
CAS number: 74-89-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 03/05/2019
Registered tonnage band: 10-100

DECISION ON A COMPLIANCE CHECK

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

1. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the analogue substance methylamine hydrochloride (CAS No 593-51-1);**

2. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance.**

You have to submit the requested information in an updated registration dossier by ***24 August 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.

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, shall 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 Wim De Coen, 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:

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

1. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier contains negative results for both these information requirements. Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for a "*mammalian cell gene mutation assay (Caspary and Myhr, 1986)*". However, this study does not provide the information required by Annex VIII, Section 8.4.3.

More specifically, this study is a pre-guideline study and conducted only without metabolic activation. In your conclusion, you have stated "*Methylamine caused the mutagenic response in a dose-related manner*". However, based on your report in "*table 1*", there is big variation among the results in the triplicate studies for each treated group for both trial 1 and trial 2. Furthermore, the average mutational factor did not increase in a dose dependent manner unlike your conclusion. Hence, ECHA considers that this study is not appropriate to conclude on the mutagenic property of the registered substance *in vitro* in mammalian cells.

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

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

ECHA notes there is a scientific rationale to test the salt of your registered substance i.e. hydrochloride salt, to clarify the mutagenic hazard of your registered substance.

In your comments to the draft decision, you agree to perform the test using either the registered substance or the analogue methylamine hydrochloride (CAS No 593-51-1).

The registered substance is extremely flammable, and there are less technical limitations (and less risks) in the execution of the test, when hydrochloric salt of monomethyl amine, instead of the registered substance, is administered to the test medium.

Hence, testing shall be performed with the analogue substance methylamine hydrochloride (CAS No 593-51-1).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: *In vitro* mammalian cell gene mutation test (test method:

OECD TG 476 *or* OECD TG 490) with the analogue substance methylamine hydrochloride (CAS No 593-51-1).

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. 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.

Column 2 of Annex VII, Section 9.1.2 specifies that the study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes.

In the technical dossier, you have provided records for two non-guideline key studies:

a) Bringmann, G., 1959, reporting a 96 hour toxic threshold concentration TTC = 4mg/L and
b) Andreozzi R., et al., 2000, reporting 21% growth inhibition at 31 mg/L

In the initial draft decision that was notified to you for your comments, ECHA found that these studies do not provide the information required by Annex VII, Section 9.1.2., due to following reasons:

a) No description of the study design and test guideline;
b) only one test concentration used; lack of analytical verification of the tested concentration;
c) N-methylamine hydrochloride (CAS 593-51-1, EC 209-795-0) was tested instead of the registered substance and no justification for read-across provided.

You have also provided in the IUCLID dossier summary of several supporting experimental studies. In this regard, ECHA found that their methods and endpoints are not comparable to the standard guidelines. Further, you have provided a 96h value for algae toxicity of 55.98 mg/L estimated with ECOSAR v1.00. ECHA noted that you have not justified why this calculation can be considered reliable.

ECHA also found that OECD SIDS Initial Assessment Report for the C1-C13 Primary Amine category (http://webnet.oecd.org/Hpv/UI/handler.axd?id=9e86965a-715b-4cb8-99a4-f7113a364ea9, last accessed 21.11.2017) in which the registered substance belongs provides a 96 h algae toxicity value of 2.25 mg/L estimated for the registered substance using ECOSAR v1.0. Because Annex I, Section 0.5 of the REACH regulation states that "*Available information from assessments carried out under other national and international programmes should be included*" in the chemical safety assessment, you should include that information on algae toxicity.

Furthermore, the OECD SIDS Initial Assessment Report for the C1-C13 Primary Amine category states that "*Small aliphatic amines are more toxic to algae than fish and invertebrates*" and "*Small aliphatic amines that are un-ionized are more toxic to fish and invertebrates than when ionized; toxicity to algae seems to be unaffected by ionization.*" Hence algae appears to be most sensitive species, while reliable data on algae toxicity is missing.

Thus, overall ECHA considered that the results of the key and supporting studies for algae

toxicity reported in the registration dossier are not adequate for the purpose of classification/labelling and risk assessment and therefore does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In your comments on the draft decision you agreed that the reporting of the literature data, including the studies by Bringmann (1959) and Andreozzi et al (2000), lack the required level of detail to assess their reliability. You also indicated that you have an updated ECOSAR Quantitative Structure-Activity Relationship (QSAR) prediction for this endpoint that you will include in next dossier update. Overall you indicated that you will update the endpoint with a weight-of-evidence (WoE) approach of the available data to fulfil the information requirement.

In your updated dossier (submission number [redacted]), you included the updated QSAR prediction as an endpoint study record. ECHA considered that the prediction fulfils the conditions set in Annex XI section 1.3. for QSARs. Therefore ECHA removed this request from the decision prior to notification to the Member State Competent Authorities (MSCAs).

However, an MSCA submitted a Proposal for Amendment (PfA) as they considered that the information submitted for this endpoint in the technical dossier and in the Chemical Safety Report (CSR) is not consistent. Due to this inconsistency the actual effect values for this endpoint are unclear. In the PfA, it was furthermore indicated that more information on the study by Bringmann (1959) was needed.

Following the PfA, ECHA notes that while the updated QSAR has been included in the technical dossier you have not reflected this prediction in the endpoint summary nor in your CSR. You have also not provided a WoE approach according to Annex XI section 1.2 to fulfil this information requirement as proposed by you in your comments on the initial draft decision. Instead you have still indicated the study by Bringmann (1959) as the key study. ECHA hence agrees with the PfA in that it is necessary to update the endpoint, both in the technical dossier and the CSR. However, ECHA would still like to note that as indicated above and in the initial draft decision, ECHA considers that with currently available information the study by Bringmann alone is not adequate to fulfil the present information requirement. The study by Andreozzi R., et al., 2000 is also not acceptable due to the short test duration.

In summary, ECHA considers that the information requirement has not yet been fulfilled.

In your comments on the PfA you agree that the endpoint needs clarification. ECHA acknowledges your intention to review all available data, in line with the PfA, to include a new read-across study with an analogue substance methylammonium chloride, and to then follow a WoE approach to fulfil the information requirement.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

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: Algae growth inhibition test, EU C.3./OECD TG 201).

Appendix 2: Procedural history

You were notified that the draft 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. However, following your comments on the draft decision and the inter-related new and substantial information provided in the updated dossier, ECHA has taken into account all the updated information, relevant, to the draft decision. Based on the average production and/or import volumes for the three preceding calendar years, ECHA has changed the tonnage band from 100-1000 tonnes per year (submission number: [redacted] submission date: 22 March 2017) to 10-100 tonnes per year (submission number [redacted] and date 03 May 2019).

The compliance check was initiated on 16 October 2017.

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, your updated dossier and amended the request(s) and the deadline.

As a result, the requests for information on Pre-natal developmental toxicity study;Extended one-generation reproductive toxicity study;Growth inhibition study aquatic plants;Exposure assessment and risk characterisation were removed. In addition, the request for information on In vitro gene mutation study in mammalian cells was modified in Appendix 1, accordingly.

Due to the removal of the above requests the deadline was amended from 30 months to 9 months.

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

ECHA received proposals for amendment and modified the draft decision. A request for information on Growth inhibition study aquatic plants was re-introduced in the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

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

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-66 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

ECHA
EUROPEAN CHEMICALS AGENCY

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.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.