Helsinki, 23 March 2017

Addressee: [redacted]

Decision number: CCH-D-2114355487-39-01/F
Substance name: 1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione
EC number: 258-904-8
CAS number: 53988-10-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 29.09.2015
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. **Description of the analytical methods (Annex VI, Section 2.3.7) for the registered substance;**
   - **Identification and quantification of the main constituent(s)**

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) 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 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 and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **3 April 2018**.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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 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.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

1. Description of the analytical methods (Annex VI, Section 2.3.7.)

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

"Description of the analytical methods" is an information requirement as laid down in Annex VI, Section 2.3.7. of the REACH Regulation. Adequate information needs to be present in the registration dossier to meet this information requirement.

You have not provided a detailed description of the analytical method used for the identification and quantification of the constituents and impurities present in the composition of the registered substance. In particular, you have not provide a chromatogram that would enable the quantification of the registered substance.

The composition reported in section 1.2 indicates that the registered substance consists of two main constituents [redacted]. Other constituents or impurities have not been reported in section 1.2.

ECHA notes that you have provided a ^{1}HNMR spectrum in section 1.4 of the IUCLID dossier (document "[redacted]") that may have been intended to be used to support the composition reported in section 1.2. However, the provided ^{1}HNMR spectrum and interpretation of the results is not sufficient to enable the quantification of the two main constituents reported in section 1.2. Therefore, the composition of the substance cannot be confirmed by the provided ^{1}HNMR analysis.

Furthermore, you have not provided any other analysis in section 1.4 that would enable the quantification of the two main constituents reported in section 1.2.

Therefore, ECHA notes that from the described analysis and interpretation of the results it is not possible to establish the concentration levels of the constituents and impurities in the actual substance as manufactured.

Therefore, the information provided is not sufficient to support the quantification of the constituents required to be reported in section 1.2.

You are accordingly requested to provide a description of the analytical methods used for the identification and quantification of the constituents and impurities required to be reported in the composition of the registered substance.

The description shall be sufficient for the methods to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made, and the results obtained.

You shall derive the composition on the basis of the most appropriate method that shall be chosen taking into account experience and knowledge of the robustness of the method used. For this purpose, you should submit an appropriate chromatographic analysis including the chromatogram and a peak table containing the retention times, peak areas and peak area % of the constituents. If other analytical methods are suitable for quantification of the constituents required to be reported in section 1.2, such methods may also be used.

When reporting the composition of registered substance you shall take into account the uncertainty of the results obtained. You shall ensure that the concentration levels of the constituents present in the substance are not underestimated.

As for the reporting of the data in the registration dossier, the information should be included in section 1.4 of the IUCLID dossier.

In your comments on the draft decision you indicated a willingness to provide the requested information.

2. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of 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* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. 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.

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

You have not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. (Grouping of substances and read-across approach) of the REACH Regulation by providing a study record for the *in vitro* Mammalian Chromosome Aberration Test (OECD TG 473) with the analogue substance, 3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione, zinc salt (EC no 262-872-0; ZMB2) - hereafter referred to as the 'source substance ZMB2' – and the following justification:

"*This result is assumed to be an effect of the of 1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione anion rather than of the hydronium ion (which is a normal constituent of body fluids) or zinc cation, which is an essential element in humans*".
In order to support this approach you have provided a data matrix presenting information on physico-chemical properties and toxicological properties on acute toxicity, skin and eye irritation, sensitisation, genotoxicty, repeated-dose toxicity, reproductive toxicity and carcinogenicity for the source substance ZMB2 and the substance subject to this decision (hereafter referred to as the 'target substance MB2)'.

ECHA has evaluated the information and documentation provided in the registration dossier in light of the requirements of Annex XI, Section 1.5 of the REACH Regulation and has the following observations:

(i) According to the provisions of Annex XI, section 1.5 of the REACH Regulation, application of the grouping and read-across concept requires that the properties of a substance may be predicted from data on another structurally similar substance.

You have presented information establishing a structural relationship between the source substance ZMB2 and the target substance MB2. Structural similarity is a prerequisite for applying the grouping and read-across approach. ECHA acknowledges that the source substance ZMB2 and the target substance MB2 are structural analogues. However, structural similarity is not per se sufficient to enable the prediction of human health properties. A read-across hypothesis establishing a basis for this prediction, and developed on the basis of structural similarity, is a fundamental aspect of a read-across approach.

(ii) ECHA notes that your read-across hypothesis relies on the assumption that the source substance ZMB2 dissociates to the same anion as the one formed from the dissociation of the target substance MB2, that is in the common 1,3-dihydro-4(or5)-methyl-2H-benzimidazole-2-thione anion. No qualitative or quantitative information characterising the dissociation of the source substance ZMB2 has been provided in the technical dossier to support this assumption. The possibility that ZMB2 remains as a stable molecule in aqueous solution cannot be dismissed and information included in the registration dossier of ZMB2 does suggest that "*ZMB2 does remain as a single molecule, at least to some degree*".

(iii) You have presented information comparing the properties of the target substance MB2 and the source substance ZMB2 in the endpoint study record for the in vitro chromosome aberration study "*rel 1-key, CA, SPL, 2005.* This information includes data presenting similarities in physico-chemical properties and similarities in multiple toxicological endpoints. You particularly refer to results from a 28-day repeated-dose toxicity study performed with MB2 and results from a combined repeated dose toxicity study with the reproduction / developmental toxicity screening study conducted with the source substance ZMB2. ECHA observes similarities between the target organs identified from these studies with effects on the thyroid and the liver. However ECHA notes that this set of information does not provide evidence supporting your hypothesis that the target substance MB2 and the source substance ZMB2 have similar properties with regard to *in vitro* cytogenicity.

Additionally, the relevance of the information generated using ZMB2 in the identification of the hazardous properties of MB2, as part of your read-across approach, cannot be confirmed due to missing information on the extent of the dissociation of ZMB2, as indicated above.

In the absence of information characterizing the rate and extent of the dissociation of the source substance ZMB2 in the 1,3-dihydro-4(or5)-methyl-2H-benzimidazole-2-thione anion and the zinc cation, ECHA considers that the information provided in the dossier does not verify your read-across hypothesis according to which the properties of the source and target substances are likely to be similar or to follow a regular pattern as a result of their structural similarity and behaviour in aqueous media.

Therefore ECHA concludes that you have not provided an adequate basis for predicting the properties of the target substance from the source substance as required by the provisions of Annex XI, section 1.5 of the REACH Regulation. As a consequence, the adaptation of the information requirement of *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study based on this read-across approach cannot be accepted.

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

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments on the draft decision you indicated a willingness to provide the requested information.

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: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

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 11 May 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 request(s).

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. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2018.

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

3. 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 your Member State.

4. In carrying out the test(s) 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 test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.