EUROPEAN CHEMICALS AGENCY

Helsinki, 23 March 2017

Addressee: [redacted]

Decision number: TPE-D-2114355514-50-01/F
Substance name: 1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione, zinc salt
EC number: 262-872-0
CAS number: 61617-00-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 10.06.2016
Registered tonnage band: 100-1000T

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

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance.**

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

2. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **At least two weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity); and**
   - **Cohort 3 (Developmental immunotoxicity);**

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 **30 September 2019**. You shall also 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. 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.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

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

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the 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 EU B.31./OECD TG 414 by the oral route.

ECHA considers that the proposed 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 EU B.31./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.

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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(a) 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 rabbits), oral route (test method: EU B.31./OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

2. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

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

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 IX of the REACH Regulation if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A and 2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

ECHA considers that adverse effects on reproductive organs or tissues and other concerns in relation with reproductive toxicity are observed in a combined repeated dose toxicity study with the reproduction / developmental toxicity screening study (OECD TG 422) conducted with the registered substance in rats via the oral route ([redacted], 2006). More specifically, impaired fertility as evidenced by a reduced mating performance, alteration of oestrous cyclicity and increased gestation length have been observed in this study. As the condition of Annex IX, Section 8.7.3. is fulfilled, an extended one-generation reproductive toxicity study is an information requirement for the registered substance pursuant to Annex IX, Section 8.7.3.

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 EU B.56./OECD TG 443 by the oral route.

You have provided the following justification and specification of the design of this study:
"*In a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD TG 422) in Sprague-Dawley rats by the oral route (diet) with ZMB2 increased liver weight and histopathology, thyroid hypertrophy and increased cholesterol were reported ([redacted], 2006). Due to these effects, the LR proposes that EOGRTS include the examination of potential endocrine related toxicity with cohort 1B extended to include the F2 generation to clarify toxicity to thyroid.*
In the OECD TG 422, statistically significant reductions in male absolute organ weight values compared to control values were observed for the thymus in all dose groups. Due to these effects, the LR proposes the EOGRTS to include the examination of potential immunotoxicological effects (cohort 3).
There are no triggers to include specific neurotoxicity examinations.
Exposure via diet:

According to OECD TG 443 and EU.56 "Dietary exposure is the preferred method of administration". Based on the complexity of this study, with extension of Cohort 1B to include the F2 generation and taking into account that the available OECD TG 422 dosed rats also via diet, diet is considered to be the appropriate dosing route."

ECHA considers that the proposed study design requires modification to fulfil the information requirement of Annex IX, Section 8.7.3. of the REACH Regulation.The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

In your testing proposal you did not specify the duration of the premating exposure period.

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 if 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* R.7.a, chapter R.7.6 (version 4.1, October 2015). In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of 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 existing 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 8.7.3., Annex IX 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 to include an extension of Cohort 1B and provided justifications not fully following the criteria described in column 2 of Section 8.7.3 of Annex IX and detailed in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

You have indicated in your testing proposal justification document that the Cohort 1B should be extended on the basis of findings in the screening study (OECD TG 422) to *"...clarify toxicity to thyroid."* However, your justification does not include any exposure considerations and other relevant toxicological findings.

ECHA notes that the use of the registered substance is leading to significant exposure of professionals (PROC 0) and consumers when handling rubber and plastic goods containing the substance as anti-oxidant. Therefore, the exposure-criteria to extend the Cohort 1B, indicated in letter (a) of column 2 of 8.7.3., Annex IX is met.

Furthermore, in addition to the thyroid toxicity that you have identified, ECHA notes that the histopathological findings in the pituitary, the alterations of the oestrous cycle and the increased gestation length observed in the screening study conducted with the registered substance are also indications of modes of action relating to endocrine disruption and therefore constitute triggers for the extension of the Cohort 1B. Therefore, the toxicity-criteria to extend the Cohort 1B, indicated in letter (b) of column 2 of 8.7.3., Annex IX is met.

ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because both conditions of column 2 of 8.7.3., Annex IX are met: the uses of the registered substance are leading to significant exposure of professionals and consumers and there are indications of endocrine-disruption modes of action for the registered substance.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

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 8.7.3., Annex IX. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You indicated in your testing proposal justification that *"There are no triggers to include specific neurotoxicity examinations"*.

However, ECHA notes that existing information on the registered substance itself derived from available *in vivo* studies shows evidence of thryoid toxicity observed in all treatment groups. The robust study summary for the screening study (OECD TG 422) conducted with the registered substance via the oral route states that *"higher grades of severity of follicular cell hypertrophy were seen in relation to treatment for rats of either sex of all treatment groups"*. You further indicated that *"The thyroid gland hypertrophy may also be a consequence of a negative feedback via enhanced metabolism of circulating thyroid hormones"*.

According to the information listed in Appendix R.7.6-2 of the ECHA *Guidance on information requirements and chemical safety assessment* R.7, chapter R.7.6 Reproductive toxicity (version 4.1, October 2015), "*relevant changes in thyroid hormone levels or signs of thyroid toxicity indicating such changes*" constitute indications of a specific mechanism/mode of action that has been closely linked to (developmental) neurotoxic effects.

ECHA concludes that the developmental neurotoxicity cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the registered substance itself.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

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 8.7.3., Annex IX.

You proposed to include Cohort 3 and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex IX and detailed in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

You indicated in your justification for the testing proposal that you considered that the significant reduction in thymus weight observed in all dose groups in the screening study conducted (OECD TG 422) with the registered substance do warrant the inclusion of the Cohort 3 in the design of the proposed study.

ECHA agrees that based on the information from the registered substance the criteria to include Cohort 3 are met.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* study on the registered substance.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

You did not specify the species for testing. According to the test method EU B.56./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 (dietary) 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision, you referred to a read-across approach proposed "*between 1,3-dihydro-4(or 5)-methyl-2Hbenzimidazole-2-thione (MB2; CAS 53988-10-6) and 1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione, zinc salt (ZMB2; CAS 61617-00-3)*". You further refer in your comments to the CoRAP justification document produced by the evaluating member state and assumes on the basis of the information from that document that "*that the evaluating member state considers a read-across between 2-mercaptobenzimidazole, MB2 and ZMB2 to be relevant for the toxicological evaluation of MB2 and ZMB2*" and that "*all information on 2-mercaptobenzimidazole, MB2 and ZMB2 are taken into account and an in depth evaluation of a potential read-across between MB2 and ZMB2 is expected to be conducted during the substance evaluation*".

ECHA points out that no reference to a read-across approach was made in the draft decision issued to you and addressing your proposals to perform a pre-natal developmental toxicity study and an extended-one generation reproductive toxicity study with the substance subject to this decision. Therefore ECHA considers that the reference to a read-across approach in your comments to this daft decision are not relevant in the context of this testing proposal examination.

You conclude in your comments that "*no vertebrate studies should be conducted on MB2 or ZMB2 before this evaluation is conducted by the evaluating member state*".
ECHA points out that the registration dossier subject to the decision issued to the registrant and the dossier update submitted on 10 June 2016 – submission number [redacted] – contains testing proposals for the information requirements of Annex IX, 8.7.2 for a pre-natal developmental toxicity study and of Annex IX, 8.7.3 for an extended one-generation reproductive toxicity study. According to Article 40 of the REACH Regulation, ECHA has the obligation to examine and to issue a decision on these testing proposals. ECHA has assessed these testing proposals and has communicated the outcome of its assessment in a draft decision issued to you. These studies will provide further information on the toxicological properties, including certain endocrine disrupting modes of action, also to be used during the substance evaluation process. In accordance with the provisions of Article 51 of the REACH Regulation, ECHA will notify the draft decision to the member states competent authorities (MSCAs). MSCAs may propose amendments to the draft decision to the Agency.

You stated in your comments that "*ECHA used inconsistent argumentation concerning a potential read-across throughout the draft decision*" and considered that "*Taking into account animal welfare, no vertebrate studies should be conducted on MB2 or ZMB before the substance evaluation is conducted by the evaluating member state.*" ECHA considers that this comment is not relevant in the context of this testing proposal examination process because the testing on the registered substance was proposed by you and agreed to by ECHA in this decision and that the particular concerns requiring inclusion of cohorts 2A, 2B and 3 stem from the information on the registered substance.

You reported in your comments that "*ECHA concluded on the study-design specifications without taking into account the CoRAP justification document on MB2 and ZMB2*" where the evaluating member state considered that it is not yet demonstrated that ZMB2 and MB2 do interfere with the activity of the thyroid-peroxidase-enzyme and the activity of the deiodinase-enzyme and that potential non-standard endocrine-disrupting-relevant tests might be required to clarify this point. You further considered that the endocrine-related adverse effects observed with the substance subject to this decision may be secondary to a non-endocrine-related toxicity, i.e. the induction of liver metabolizing enzymes. You concluded that an assessment of reproductive toxicity and potential direct endocrine disrupter activity or indirect endocrine-related adverse effects and a decision on the number and design of EOGRTS to be conducted should occur during the Substance Evaluation process.

ECHA observes that the standard information requirements for both the pre-natal developmental toxicity study and the extended one-generation reproductive toxicity study (EOGRTS) are required to be met for compliance under REACH. These studies have been proposed by you and the testing proposals are still included in the updated dossier submitted on 10 June 2016 – submission number [redacted].

ECHA clarifies that the design of the EOGRT study requested in the draft decision under consideration has been established on the basis of the information provided in the registration dossier with submission number [redacted] and maintained in the updated dossier with the submission number [redacted]. ECHA considers that the information reported in the CoRAP justification document does not provide reason to change the requested study design, as that information supports the concern that is related to thyroid effects.

Hence, the proposed studies are necessary to fulfil the information requirements under REACH Regulation and will provide further information on toxicological properties of the substance, including certain endocrine disrupting modes of action to be used also during substance evaluation process.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision:
Extended one-generation reproductive toxicity study (test method EU B.56./ OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 14 May 2013.

ECHA held a third party consultation for the testing proposal(s) from 15 April 2014 until 30 May 2014. ECHA did not receive information from third parties.

This decision does not take into account any updates after **8 August 2016**, 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 and did not amend the requests.
You updated your registration on 10 June 2016. 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. The substance subject to the present decision is provisionally listed on the Community rolling action plan (CoRAP) for start of substance evaluation in 2018.

2. 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.

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 the Member States.

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.