~~Confidential~~

Helsinki, 10 January 2022

Addressees
Registrant(s) of JS_Accelerator ZMBT as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
16/09/2020

Registered substance subject to this decision ("the Substance")
Substance name: Zinc di(benzothiazol-2-yl) disulphide
EC number: 205-840-3
CAS number: 155-04-4

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By the above-mentioned decision of 14 September 2018 (the "original decision") ECHA requested you to submit information by 21 September 2020 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the "REACH Regulation"), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

Your registration still does not comply with the following information requirement(s):

A. Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance-modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy;

2. 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 with the registered substance.

You are therefore still required to provide this information requested in the original decision.

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annexes IX of REACH".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision and exercise the powers reserved to them under Article 126 of Regulation No 1907/2006 (penalties for non-compliance)[1].

Authorised[2] under the authority of Mike Rasenberg, Director of Hazard Assessment

[1] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA

[2] 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 on Reasons common to several requests

1. Assessment of your read-across approach under Annex XI, Section 1.5.

i. Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[3,4].

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 7. Furthermore you have provided an expert statement "Information/Assumptions regarding Toxicokinetics: Zinc 2-Mercaptobenzothioazole (CAS No 155-04-4; EC No 205-840-3)" (2020).

You read-across between the structurally similar substances 2-Mercaptobenzothiazole (MBT, EC 205-736-8) and Zn^{2+} ions as source substances, and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties:

"The read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed." … "It can thus be expected that systemic toxicity after oral treatment of experimental animals with high ZMBT doses are a consequence of the toxic properties of the systemically available MBT." …

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products.

Secondly, ECHA understands that you also argue that the hazardous properties of your

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

Substance can be predicted from information on the analogue substance MBT, i.e. a read-across hypothesis which assumes that different compounds have the same type of effects.

The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA notes the following shortcomings with regards to prediction of toxicological properties.

Read-across hypothesis contradicted by existing data

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The ECHA Guidance[1] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*".

The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s). The observation of differences in the intrinsic properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence.

As indicated above, your read-across hypothesis is based on the assumption of formation of common (bio)transformation products, but also that the structurally similar target and source substances cause the same type of effect(s) because the systemic toxicity of your Substance is a consequence of the toxic properties of the systemically available MBT.

<u>Hydrolysis of the Substance</u>
Regarding hydrolysis, in your updated dossier you have provided a study record for the study "Determination of the hydrolysis of (EC 205-840-3; CAS 155-04/4) ZMBT" (2019). The study is described as follows:

"The test item was dissolved to the maximum reachable solubility (saturated solution) at a preferably neutral pH-value. After filtration of undissolved particles 1H-NMR spectra were recorded and the presence of the test item could be confirmed." … "The filtered solution was then acidified with deuterated acetic acid to decrease the pH to approx. 3." … "The test solution was then repeatedly measured by 1H-NMR." … "As no remaining signals derived from ZMBT after acidification were observed, it was concluded that all ZMBT used in the sample is immediately hydrolyzed under acidic conditions to MBT (complete but unquantifiable after filtration) in less than 9 minutes."

To support your read-across hypothesis based on (bio)transformation, you have demonstrated that the water soluble fraction of your Substance is hydrolysed to MBT and Zinc cations.

However, there is an unquantified amount of undissolved particles of the Substance which is not hydrolysed. This observation is still valid despite the new information on water solubility reported in your comments to the draft decision (for details see below). This contradicts your

[1] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

claim whereby the Substance is rapidly and quantitatively converted into the source substance(s) and exposure to the parent compound ZMBT needs to be assessed.

Absorption and systemic exposure of your Substance (parent compound)
Regarding absorption of your Substance (exposure to the parent compound) you have provided an expert statement "Information/Assumptions regarding Toxicokinetics: Zinc 2-Mercaptobenzothioazole (CAS No 155-04-4; EC No 205-840-3) (2020). In this document the expert concludes the following on exposure to the parent compound:

"…….absorption of the hydrolyzation product MBT with a MW of 167.25 and a log P of 2.42 can be expected in experimental settings. This view is supported by toxicokinetic investigations and by signs of systemic toxicity after oral treatment of experimental animals with high MBT doses.

On the other hand the physical-chemical properties of ZMBT are not favourable for absorption in the gastro-intestinal tract, with a MW of 397.9, a calculated log P of 5.2 and the proof of complete hydrolysis at acid pH values. It can thus be expected that systemic toxicity after oral treatment of experimental animals with high ZMBT doses are a consequence of the toxic properties of the systemically available MBT."

In your registration dossier (Section 7.1.1, data matrix 1) you reported the water solubility of the Substance as 20.6 mg/ml at 20°C and pH 6.3 and of the source substance MBT (EC 205-736-8) 118 mg/ml at 25°C and pH 7.

In your comments to the draft decision you provide new information for water solubility and log Kow of the Substance, 91.79 mg/L and 0.05, respectively.

Based on information on physico-chemical properties of the target and the source you argue in your expert statement that "*It can thus be expected that systemic toxicity after oral treatment of experimental animals with high ZMBT doses are a consequence of the toxic properties of the systemically available MBT".* There is however no toxicokinetic data for your Substance to support this conclusion.

As indicated above, the water solubility of the Substance determines which fraction of the test material would be subsequently dissociating into the source substances Zinc cations and MBT. This fraction is small, also with the corrected figure for water solubility which you provided with your comments on the draft decision.

On the basis of the information from your registration dossier, it cannot be ruled out that the parent compound will pass on into the intestine and there be absorbed under conditions favourable for substances of higher partition coefficients. Regarding the information provided with your comments to the draft decision, indicating a lower log Kow than that originally presented, this information would lower the possibility for intestinal uptake. However, it might instead favour uptake of the parent compound in the stomach.

Based on the above there is uncertainty related to absorption of the Substance and the source substance in the gastro-intestinal tract, and you have still not demonstrated and justified that the properties of the source substance and of the Substance are likely to be similar.

Supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting*

information to strengthen the rationale for the read-across"[5]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting information must include toxicological information to allow comparison of the hazard profiles for the target and the source.

As indicated above, your second read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

You provided with your current dossier update the same studies with the source substances as with the technical dossier evaluated by ECHA when it came to its original decision. You did not provide any studies with the Substance for repeated dose toxicity and reproduction toxicity.

Therefore, the data set reported in the technical dossier still does not include relevant, reliable and adequate information for the Substance to support your read-across hypothesis.

In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

The source studies that you have used in your read-across approach were evaluated by ECHA in the original decision. As the same studies have been provided in the submission subject to this decision the shortcomings identified in the original decision remain. These include in particular issues relevant to the endpoint repeated dose toxicity study (90-day), such as dose setting, adequate and reliable coverage of the key parameters, and data reporting. However, in the comments to the draft decision, you agree to perform an OECD TG 408 study as requested in this decision.

In addition, to support the risk assessment of your Substance, you were requested to include in your OECD TG 408 study urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy. This data has not been submitted.

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

Appendix A: Reasons to request information required under Annex IX of REACH

1. Sub-chronic toxicity study (90-day)

You were requested to submit information derived with the registered substance for sub-chronic toxicity study (90-day).

In response, you provided: the same information with analogue substances as already evaluated by ECHA in the original decision.

As explained in the Appendix entitled "Reasons common to several requests" your adaptation according to Annex XI Section 1.5. is still rejected. In the comments to the draft decision, you agree to perform the requested study.

Therefore, the information you provided does not fulfil the information requirement and you are still required to provide Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance, modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

2. Pre-natal developmental toxicity study in a first species

You were requested to submit information derived with the registered substance for pre-natal toxicity in a first species.

In response, you provided: the same information with an analogue substance as already evaluated by ECHA in the original decision.

In your comments to the draft decision you have included some information to strengthen your read-across approach, and you explain that you will further improve its basis with additional experimental information.

However, as explained in the Appendix entitled "Reasons common to several requests" your adaptation according to Annex XI Section 1.5. is still rejected. Therefore the data gap remains.

Therefore, the information you provided does not fulfil the information requirement and you are still required to provide 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 with the registered substance.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[6].

B. Test material

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

Appendix C: Procedure

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision of 14 September 2018 ("the original decision"). Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 16 November 2020.

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 adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance[8] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[9]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[10]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[11]

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[11] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.