EUROPEAN CHEMICALS AGENCY

Helsinki, 23 September 2016

Addressee: [redacted]

Decision number: CCH-D-2114343759-36-01/F
Substance name: di(benzothiazol-2-yl) disulphide
EC number: 204-424-9
CAS number: 120-78-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27.11.2012
Registered tonnage band: [redacted]

DECISION ON A COMPLIANCE CHECK

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

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance; alternatively an available pre-natal developmental toxicity study in the rabbit with the analogue substance benzothiazole-2–thiol (MBT);**

2. **Human data on carcinogenicity (Annex I, Section 1.0.3 and Section 1.2) for the analogue substance benzothiazole-2–thiol (MBT);**

3. **Available international assessments (Annex I, Section 0.5) for the analogue substance benzothiazole-2–thiol (MBT).**

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 **2 October 2017**. You shall also update the chemical safety report, where relevant.

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 Hannu Braunschweiler, Head of Unit, Evaluation E1

[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

0. Grouping of substances and read-across approach

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".

In the registration, you have adapted standard information requirements by applying a read-across adaptation following REACH Annex XI, Section 1.5.

As explained below ECHA accepts the read-across adaptations. Annex XI Section 1.5 provides "*if the group concept is applied, substances shall be classified and labelled on this basis*" and "*...the results should be adequate for the purpose of classification and labelling and/or risk assessment*". With regard to these provisions all relevant information for the analogue substance benzothiazole-2–thiol need to be included in the dossier and must be considered in the chemical safety assessment for the registered substance di(benzothiazol-2-yl) disulphide.

0.1 Description of the grouping and read-across approach proposed

You have proposed to predict properties of the registered substance di(benzothiazol-2-yl) disulphide (named MBTS in the following text) from the source substance benzothiazole-2 – thiol (named MBT in the following text). Your scientific reasoning is that MBTS consists of two MTB moieties; and that MBTS is readily converted to MBT. The read-across hypothesis, thus, relies on the formation of breakdown products from MBTS which are chemically identical to the source substance MBT.

ECHA considers this as the hypothesis under which you make predictions for the properties listed above.

0.2 Support of the grouping and read-across approach

You have provided a read-across justification in the toxicokinetics section of the CSR (section 5.1.3).

Furthermore you have provided a data matrix for MBTS and MBT containing physico-chemical properties as well as information on acute toxicity, skin and eye irritation, skin sensitisation and mutagenicity. Also information on hydrolysis is provided. In addition, the results of a toxicokinetics study with MBT and MBTS are provided as supporting evidence. In summary you provide the following arguments to support the read-across approach:

- For hydrolysis you note: "*According to expert justification, the conversion of MBTS to MBT takes place only under reductive condition and hence with the presence of oxygen MBTS is considered as stable in aqueous solution. This has been proved by Hansson & Agrup (1993) with negligible dissipation of MBTS observed in the buffer solution of pH6.5.*

Increased dissipation of MBTS with metabolites like MBT (149-30-4), BT (95-16-9) and BTon (934-34-9) was observed under increased temperature and pH (e.g. 6.7 % dissipation of MBTS at pH 9.8 and 58 °C in 65 hours) and decreased particle size present in the aqueous solution. In conclusion, MBTS is considered as hydrolytically stable under environmental relevant pH and temperatures with the presence of dissolved oxygen in aqueous solution."

- For hydrolysis is additionally provided: "*Hansson & Agrup (1993) analyzed test solutions containing 500 µM (170 mg/l) MBTS in 0.5 M phosphate buffer and 10% tetrahydrofuran at pH 6.5. After 2 hours reaction time a sediment of MBTS was formed and only trace amounts of MBTS were converted to MBT. After addition of the reducing agent gluthathione, MBT was formed quantitatively within 10 minutes. When the same experiment was run with a MBT solution, 60% were converted to MBTS without gluthathione after 2 hours, while after gluthathione addition MBT was stable. The results reveal that the equilibrium between MBT and MBTS is largely influenced by the redox status of the medium.*" (EU RAR 2008, N-Cyclohexylbenzothiayol-2-sulphenamide, Appendix B)
- (CMA 1986). A toxicokinetic study in F344 rats with radioactive labelled 14C-MBTS in F-344 rats demonstrated the uptake and a biphasic elimination. More than 50 % of absorbed radioactive label was excreted after 24 hours. Two main metabolites, and five not identified metabolites, but no MBTS, were detected in the urine.
- El Dareer (1989). A comparison of the toxicokinetic characteristics of radioactive labelled MBTS and MBT was conducted in F-344 rats and Hartley guinea pigs. The elimination kinetics, as well as the metabolite profiles in the urine, were similar after MBTS and MBT administration. No MBTS was detected. A thioglucoronide and probably a sulfonic acid derivative of MBT were detected after MBTS and MBT administration.
- El Dareer (1989). Toxicokinetics information after intravenous and dermal application confirm that the major excretion pathway is urine and that dermal uptake is below 10 % of the radioactivity applied.
- For the data matrix you note: "*The available physico-chemical data and mammalian toxicity data from MBTS were compared with data from MBT (see table data matrix). Similarities in mammalian toxicity were noted in MBT and MBTS treated animals. Both substances showed a non skin- and eye irritating potential in rabbits. For both substances a moderate skin sensitizing potential was revealed. The oral and dermal acute toxicity of MBTS and MBT is very low, indicated by oral LD50 values of >= 3800 mg/kg bw rat and dermal LD50 values > 7940 mg/kg bw. Overall, no mutagenic potential was indicated for MBTS and MBT in bacterial mutation assays.*"

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0.3 ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

(i) Explanation on why and how the structural similarities allow predictions

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.
ECHA notes the following observations:

a. Under an existing chemicals program in Germany[2] MBT data were used to assess the MBTS properties. The main argument was that MBTS and MBT are in redox equilibrium, *i.e.* depending on the redox status of the medium MBTS will be present as MBTS or MBT. This argument is in line with the hydrolysis information when glutathione is added.

b. The proposed source substance MBT has been evaluated in a recent EU Substance Evaluation (2014)[3]. The evaluating Member State concluded that the information for MBT is sufficient for the evaluation and the assessment of the human health related toxicity profile. In a very recent IARC publication (2016)[4] it was communicated that MBT is classified as a carcinogen (group 2 A) by IARC.

c. The toxicokinetics information comparing MBTS and MBT in rats and guinea in studies with oral administration provide support to the hypothesis that MBTS is converted *in vivo* to MBT. No metabolite indicating non-converted MBTS has been identified. The elimination kinetics of MBTS and MBT were similar in rats and guinea pigs.

d. You have explained that MBTS is rapidly converted to MBT. It is not explained what the mechanism of the conversion is. However, ECHA considers it plausible that - whatever the specific mechanism is - the thiol and/or the disulphide are present in biological systems dependent on the redox status of the medium. In the presence of glutathione mainly MBT is expected to be present. The information on toxicokinetics comparing the uptake and elimination of MBT and MBTS in rats and guinea pigs confirm this expectation.

[2] BUA Stoffbericht 126, 1993
[3] http://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e5b5a
[4] https://www.iarc.fr/en/media-centre/iarcnews/pdf/QA%20on%20MBT.pdf; http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2816%2900137-6/fulltext

(iii) Support of a similar or regular pattern as a result of structural similarity

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.* One prerequisite for a prediction based on read-across therefore is that the substances involved are structural similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

ECHA notes the following observations:

a. The data matrix presented does not contradict the hypothesis under which you make predictions.

b. There is a pre-natal developmental toxicity study available in the dossier conducted with MBTS administered via the diet in the rat (doses tested: 0, 26, 127, and 596 mg/kg bw/day; Ema, 1989). In this study, no adverse effects on the offspring were noted up to the highest dose tested. Maternal toxicity was observed at the highest dose by a reduction of body weight during day 0 to 14 of pregnancy. The MBTS study also had a separate module to test for postnatal toxicity of the offspring (up to 21 days after birth). No adverse effects were noted and the autopsy of the sacrificed offspring revealed no treatment related findings. The corresponding study results with MBT which would allow a comparison with the results obtained with MBTS are not present in the dossier. ECHA observes that in the EU Substance Evaluation Report on MBT[4] it is described for MBT that no evidence of pre-natal developmental toxicity was observed in rats with a maternal NOAEL of 300 mg/kg bw/day and a developmental NOAEL of 1800 mg/kg bw/day. These results confirm that the PNDT studies with MBTS and MBT in the rat resulted in similar outcomes.

ECHA concludes that the presented evidence for studies conducted with MBTS does not contradict a similar or regular pattern of toxicity of MBT and MBTS as a result of structural similarity.

0.4 Conclusion on the read-across approach

ECHA considers the read-across justification to be a basis to predict properties of the registered substance for the reasons set out above.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) 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 oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

As explained above, the information provided 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.

The test in the first species was carried out by using a rodent species (rats). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbits as a second species.

ECHA considers 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 agreed to include in the registration dossier the available information on pre-natal developmental toxicity in rabbits conducted with the analogue substance MBT.

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: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit) by the oral route. As an alternative, and based on the read-across adaptation applied between MBT and MBTS as addressed above, an existing pre-natal developmental toxicity study in a second species (rabbit) for MBT may be provided.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species with the registered substance you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. ECHA notes that in the EU Substance Evaluation report on MBT (2014)[4] there is a pre-natal developmental toxicity study in rabbits described which was conducted with the proposed analogue substance MBT. You should consider whether this study may be provided instead of conducting a new experimental study on MBTS. In case a new experimental study is conducted the reasons for not providing the existing study on MBT should be added to the updated registration dossier.

2. Human data on carcinogenicity (Annex I, Section 1.0.3 and Section 1.2)

Pursuant to Articles 10(a) and Annex I of the REACH Regulation, a technical dossier registered at [redacted] per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation and the available human information.

In the dossier there is no information on the carcinogenic effects observed in humans of the registered substance or the proposed source substance. In the CSR you state that such information is not available. The EU Substance Evaluation report on MBT (2014)[4], however, decribes the available epidemiological studies on two occupational cohorts from plants with MBT manufacture (Strauss *et al.*, 1993; Collins *et al.*, 1999, Sorahan and Pope, 1993; Sorahan et al. 2000, Sorahan 2008, 2009). Since you have proposed MBT as source substance for your registered substance and ECHA accepts the proposed read-across to this substance, the human information is highly relevant for the assessment of the possible carcinogenic effects of MBTS, which is converted to MBT.

In your comments to the draft decision you agreed to include in the registration dossier the available human data on carcinogenicity for the analogue substance MBT.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the analogue substance: results of the available epidemiological studies on occupational cohorts in plants with a history of MBT manufacture (Strauss *et al.*, 1993; Collins *et al.*, 1999, Sorahan and Pope, 1993; Sorahan *et al.* 2000, Sorahan 2008, 2009).

3. Available international assessments on the analogue substance proposed for read-across. (Annex I, Section 0.5)

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report (CSR) which shall document the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation. Pursuant to Annex I, Section 0.5. of the REACH Regulation "*Available information from assessments carried out under other international and national programmes shall be included.*"

ECHA notes that you have proposed to use a read-across approach for MBTS based on the analogue substance MBT and, as explained in section 0 of this appendix, ECHA accepts this approach. Therefore, international assessments conducted on basis of data that you rely upon for many human health endpoints in order to achieve dossier compliance for MBT are of relevance to the dossier of the registered substance MBTS and must be included in the CSR.

For MBT there is an EU Substance Evaluation report and conclusion available (2014)[4]. The evaluating Member State concludes that "*After the results of the monitoring programme (Section 2) are available a Risk management Options Analysis (RMOA) is envisaged by the evaluating member state.*"

Furthermore, there is a recent IARC assessment available for MBT[5]."*The working group of Volume 115 of the IARC Monographs classified MBT as probably carcinogenic to humans (Group 2 A) based on limited evidence of carcinogenicity in humans that it causes bladder cancer and sufficient evidence of carcinogenicity in experimental animals.*" ECHA notes that the Volume 115 of the IARC monographs is not yet available. However, due to the relevance of the information ECHA expects an update of the dossier without undue delay after the IARC monograph has been published which includes the information IARC has used for the assessment and the conclusions drawn.

In your comments to the draft decision you agreed to include in the registration dossier the available international assessments for the analogue substance MBT. ECHA notes that the registration dossier and the CSR needs to be updated as soon as the full documentation in IARC Monograph 115 is available to consider the consequences of IARC's assessment for the registered substance.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation you are requested to include the results of the available EU Substance Evaluation report (2014) on the proposed analogue substance MBT and its conclusions as well as the IARC assessment on MBT and its conclusions in the CSR. The results need to be assessed for relevance with regard to the registered substance.

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 30 March 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.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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 proposed analogue substance was listed in the Community rolling action plan (CoRAP) and has been evaluated in 2013.

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 relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) 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 test(s) to be assessed.