EUROPEAN CHEMICALS AGENCY

Helsinki, 14 September 2018

Addressee: [redacted]

Decision number: CCH-D-2114440105-63-01/F
Substance name: zinc di(benzothiazol-2-yl) disulphide
EC number: 205-840-3
CAS number: 155-04-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11/07/2017
Registered tonnage band: [redacted] (submission number [redacted] with latest tonnage band)

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 bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14./OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

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;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance provided that both studies requested under 1. and 2. have negative results;**

4. **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;**

5. **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 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 to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **21 September 2020**. You also have to 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 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, has to 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 Claudio Carlon, Head of Unit, Evaluation E2

[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

TOXICOLOGICAL INFORMATION

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

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 2 to 7).

Grouping of substances and read-across approach

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological 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 (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical properties influence the human health properties of a substance and should be considered in read-across assessments. However, the information on physicochemical properties is only a part of the read-across hypothesis, and it is necessary to provide

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar toxicological properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

i. Description of the grouping and read-across approach proposed by you

You consider to achieve compliance with the REACH information requirements for the registered substance zinc 1,3-benzothiazole-2-thiolate (EC number 205-840-3, CAS RN 155-04-4) using data of the structurally similar substance 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4) (hereafter the 'source substance') and Zn^{2+}.

You have provided a read-across justification under section 7.1. of the IUCLID dossier, displayed in three endpoint study records, covering MBT in the first two and Zinc in the third. More specifically, you have referred to the 'EU risk assessment (2004)' (European Union Risk Assessment Report on zinc metal, CAS: 7440-66-6; EINECS No: 231-175-3). ECHA notes that this information on the read-across approach is also reported under Section 5.1.3. of the CSR.

You use the following arguments to support the prediction of properties of the registered substance from data for the source substance: You suggested that the registered substance (mass content ZMBT: [redacted]% MBT and [redacted]% Zn^{2+}) will dissociate into 1,3-benzothiazole-2-thiol and Zn^{2+}, and you make the assumption *"that after intake all zinc compounds (including metallic zinc) are changed (at least in part) to the ionic species and that it is zinc cation that is the determining factor for the biological activities of the zinc compounds"*. On this basis, you suggested that you can predict the properties of the registered substance from the individual components (i.e. 1,3-benzothiazole-2-thiol and Zn^{2+}). Therefore you consider that you can use this read-across approach to predict the toxicological properties of the registered substance, relying on the information from the source substance, 1,3-benzothiazole-2-thiol.

As an integral part of this prediction, you propose that the source and registered substances have similar toxicological properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

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

With regard to the proposed predictions ECHA has the following observations:

The substance characterisation of the source substance need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA's Practical Guide on "How to use alternatives to animal

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

testing to fulfil your information requirements" (chapter 4.4), it is recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* (version 2.1, May 2017) also for the source substance. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes. Currently the identity of the source substance (and its impurity profile) is not detailed in the registration dossier.

Your adaptation argument relies on the fact that the properties of the registered substance can be predicted from the properties of the dissociated organic moiety (1,3-benzothiazole-2-thiol) and Zinc ions (Zn^{2+}). Consequently you have sought to address the information requirements of the registered substance by submitting information on the source substances. Thus ECHA considers that it is implicit in your adaptation argument that the registered substance dissociates to the source substances rapidly, and so the organisms are only exposed to the source substances.

In addition, for the inorganic moiety (Zn^{2+}) you make a reference to the 'EU risk assessment (2004)' report and state that it is the zinc cation that is the determining factor for the biological activities of the zinc compounds. However, you only provided limited information on the inorganic moiety (Zn^{2+}) for human health endpoints in the technical dossier and, specifically, you have not provided endpoint study records for each endpoint which can be read-across. For this reason, you have not provided adequate and reliable documentation of the applied method, as required by Annex XI, 1.5.

Further ECHA considers that you have not clearly set out your read-across for the zinc ion in an endpoint-specific way and you have not considered any toxicokinetic or toxicodynamic interactions between the 1,3-benzothiazole-2-thiol and Zinc ions. For these reasons also ECHA considers this read-across hypothesis is not a reliable basis for predicting the properties of the registered substance. Furthermore, ECHA notes that, for your read-across to be accepted, while respecting data sharing rights of the data owner, your dossier shall contain all necessary information from the Zn^{2+} studies.

While ECHA considers it plausible that zinc 1,3-benzothiazole-2-thiolate may dissociate to form 1,3-benzothiazole-2-thiol and Zn^{2+}, you did not provide any quantitative information on this dissociation process. ECHA notes that you have provided a robust study summary to address dissociation. However this study did not follow any recognized guideline and was conducted on the source substance, 1,3-benzothiazole-2-thiol. Hence, it does not provide any relevant information in relation to the dissociation of the registered substance.

Accordingly, your technical dossier does not contain the necessary information to exclude exposure of the organisms to the registered substance (and not just as the dissociated ions), and your read-across hypothesis predicts the properties of the registered substance only on the basis that it is wholly dissociated to the component parts. Further, you have not shown that there are not differences in toxicokinetics between the registered substance and the two source substances. In particular, ECHA notes that quantitative or qualitative differences in absorption, distribution, metabolism or excretion could potentially lead to different toxicity between the registered and source substances. Therefore your read-across basis fails to reliably predict the properties of the registered substance because (a) you have not demonstrated that there is in fact complete dissociation to the individual sources substances in a sufficiently rapid manner, and there is no basis to predict the properties of the undissociated parent substance, and (b) you have not excluded toxicokinetic differences between the source and registered substances that could affect the toxicity.

Therefore, ECHA considers that read-across approach does not provide a reliable basis

whereby the human health effects of the registered substance may be predicted from data on the source substance. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. Accordingly, the analogue approach is rejected.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties. In addition, your justification should include sufficient information to reject any significant effect of the metal moiety on the predictions.

Finally, Annex XI, Section 1.5 provides with regard to the reliability and adequacy of the source studies that in all cases the results of the 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, and*
- *adequate and reliable documentation of the applied method shall be provided.*

In your comments to the draft decision you propose to do experimental investigations on the dissociation process to obtain quantitative data and to gain any toxicokinetic or toxicodynamic information on the interactions between MBT and zinc ions in order to improve the read-across approach and perform animal studies when the read-across cannot be justified.
ECHA welcomes your intention to do additional experimental investigations to clarify the dissociation process and to gain more toxicokinetics or toxicodynamic information to improve the read-across approach as already described above in this decision.

ECHA however notes that for the purpose of the decision-making, this decision does not take into account any updates submitted after 12 December 2017 that is after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after ECHA had sent the final decision).

iii. Conclusion on the read-across approach

The adaptation of the standard information requirements, namely *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.), *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.), pre-natal developmental toxicity study (Annex IX, Section 8.7.2.), extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.), in the technical dossier is based on the proposed read-across approach from the analogue substance, 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4). For the reasons as set out above, ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance.

ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health effects may be predicted from data of the source substances. Thus, the

adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.
You have provided tests on the registered substance from the years 1977, 1980 with reliability scores of 2 and from the years 1981 and 1984 with reliability scores of 4. They were not performed according to OECD TG 471 or to GLP standard.
The reliability 2 tests used four different strains of *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guideline, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

Therefore, 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.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to complete the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 and the registered substance.

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

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.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex VIII, Section 8.4.2., column 2 by providing a non-guideline, non GLP *in vivo* chromosomal aberration study (publication, 2000, reliability 2) in mice via the intraperitoneal route with the registered substance.

Use of existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) is an adaptation according to Annex XI, 1.1.2, so long as the conditions therein are fulfilled. In particular, there must be adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3) (condition (2) of section 1.1.2. of Annex XI). However, the provided study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3); specifically the study design does not follow the current test guidelines e.g. sampling is performed only once, testing is not done up to limit dose, the mitotic index is not determined as a measure of cytotoxicity and bone marrow exposure is not demonstrated. Thus condition (2) of Annex XI, 1.1.2 is not satisfied and the study cannot be accepted. Accordingly, your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.7.2., column 2 because the provided in vivo study is not a valid study according to Annex XI, 1.1.2.

Therefore, your adaptation of the information requirement is rejected.

You have also sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a supporting *in vivo* micronucleus test comparable to guideline study (no GLP) (1984, reliability 2) with the analogue substance 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4) in mouse. You also provided a supporting non-guideline non GLP dominant lethal assay/ *in vivo* mammalian germ cell study (1989) with the analogue substance 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4) in rats.

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach", your adaptation of the information requirement is rejected.

In addition, ECHA notes that since the test was conducted, significant changes have been made to OECD TG 487 and 478. Therefore, ECHA considers that the provided studies do not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation. Therefore, 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.

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.

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).

3. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a non-guideline HGPRT assay (1984) in CHO cells with the analogue substance: 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4). You also provided an OECD 476 GLP study with the analogue, 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4) in mouse lymphoma L5178Y cells (tk locus and microwell method). Both tests had negative test results.

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach", your adaptation of the information requirement is rejected.

Finally, while you have not explicitly claimed an adaptation, you have provided information on a non-guideline non GLP *Saccharomyces cerevisiae* strain D4 -mutation test, performed with the registered substance in strain D4. However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex VIII, Section 8.4.3.., column 1 because this study is not an adequate *in vitro* gene mutation assay in mammalian cells.

Therefore, your adaptation of the information requirement is rejected.

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.

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.

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 cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under 1. and 2. have negative results.

4. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a two-generation study from 1990, according to EPA final test rule FR 53 No.173 and GLP with a reliability score of 1 on the analogue substance 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4). You provided several other repeated dose studies with the analogue substance, 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4): two carcinogenicity studies (103w, 1988)) similar to OECD TG 451 with exceptions, in rats and mice; a combined repeated dose and carcinogenicity (20 months, publication, 1989), no guideline, in mice; 2 sub-chronic toxicity (13 weeks): oral, no guideline, in rats (1981) and mice (1988). You also submitted a summary of the sub-chronic toxicity information (oral route) from the EU-risk assessment (2004) on Zinc2+ (EC number 231-175-3, CAS RN 7440-66-6).

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach", your adaptation of the information requirement is rejected.

Furthermore these studies present several deficiencies, ranging from the dose setting, adequate and reliable coverage of the key parameters and data reporting. More specifically, ECHA notes that there are several key parameters in the Test Guideline for a 90-day study (i.e. the OECD TG 408) which are not covered in the two-generation study, i.e. the oestrus cycle and sperm parameters were not evaluated, and detailed clinical observations, ophthalmological examination, functional observations, haematology and clinical biochemistry and histopathology findings are not reported.

For the two carcinogenicity studies, administered via oral route ECHA notes that only two dose levels were evaluated, whereas the 90-day study guideline 408 requires three dose groups. Furthermore, the test substance should be administered daily (seven days/week) according to OECD TG 408 (or 451) while in the studies it was administered five days/week. The combined repeated dose and carcinogenicity study lacks clinical observations, ophthalmological examination, functional observations, haematology and clinical biochemistry and full histopathology which would be required from an OECD TG 408 (90-day study).

In addition you have provided a supporting study record for a chronic study (18 months, 1968, no test guideline, no GLP) with the registered substance in mice via the oral route, more specifically administered by gavage (days 7-28 of age) and in diet (after 28 days of age). ECHA notes that 18 animals/ sex/ dose were used in the study, no results were reported in the IUCLID dossier besides the conclusion "*no significant increase in tumors*". This study does not provide the results of clinical observations, ophthalmological examination, functional observations, haematology and clinical biochemistry and full histopathology which would be required from an OECD TG 408 (90-day study).

According to Annex XI, 1.1.2, experiments not carried out according to GLP or the test methods referred to in Article 13(3) must meet the four conditions specified therein. In particular, there must be adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3) (condition (2) of section 1.1.2. of Annex XI) and adequate and reliable documentation of the study is provided (condition (4)).

Specifically, there is a failure to provide adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), as explained above.

Furthermore, ECHA notes that a robust study summary is required under Article 10(a)(vii), and ECHA considers that the information provided in the endpoint study record does not meet the requirements of a robust study summary, as defined in Article 3(28). Specifically, the endpoint study record does not provide any results apart from the statement above. ECHA has provided a practical guide for "How to report robust study summaries", available at:
http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf. ECHA considers there is not sufficient information to make an independent assessment of the study minimising the need to consult the full study report, and accordingly considers that for this study, you have also failed to meet the requirement of both condition (4) of Annex XI, section 1.1.2 and of Annex XI, Section 1.5. (which requires that adequate and reliable documentation of the applied method shall be provided). Therefore this study does not meet the requirements of Annex XI, 1.1.2 .

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.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the substance is reported to occur as a dust with a significant proportion (>[redacted]% on weight basis) of particles of inhalable size (MMAD < 50 µm), according to the Chemical Safety Report, risk management measures are in place to prevent exposure of humans via inhalation. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

In addition, in the two-generation study from 1990, on the analogue substance, present in your registration dossier, adverse effects *"an increased incidence of [...] and alpha 2 µ-globulin inclusions in the proximal convoluted tubules [...]"* were observed in the kidneys of male rats and not in female rats. The fact that these effects were only observed in male rats in a structurally related substance gives rise to a concern that the registered substance may induce alpha-2u-globulin-mediated nephropathy, especially since you propose that the registered substance will dissociate into the analogue substance in vivo. ECHA accordingly considers that the kidney is a target organ of the registered substance. Since humans do not excrete alpha-2u-globulin and this mode of action is considered not relevant to humans the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment. For these reasons, ECHA considers that urinalysis is required to investigate kidney function (which is optional in

paragraphs 3, 30 and 32 of OECD TG 408, and the relevant part of Section 1.5.2.2. of EU Method B.26.). Additionally, a full histopathological examination (paragraphs 3, 35 and 36 of OECD TG 408, Section 1.5.2.4. of EU Method B.26.), which is to include immunohistochemical investigation of renal pathology needs to be performed, to determine whether the pathology is indeed mediated by alpha-2u globulin.

According to the EU B.26./OECD TG 408, the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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: Sub-chronic toxicity: 90-day study oral toxicity study (test method: EU B.26./OECD TG 408) in rats. The test shall be modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology.

Note for your consideration

ECHA notes that a revised version of OECD TG 408 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a developmental toxicity study (similar to OECD TG 414) with the analogue substance 1,3-benzothiazole-2-thiol (EC number 205-736-8, CAS RN 149-30-4) in rat.

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach", your adaptation of the information requirement is rejected.

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.

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 assumption ECHA considers testing should be performed with rats or rabbits as a first 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 6.0, July 2017) Chapter R.7a, Section 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 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 first species (rat or rabbit) by the oral route.

Note for your consideration

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 42 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.) and an Extended one-generation reproductive toxicity study in rats (Annex X, Section 8.7.3.). As these studies are not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

In addition, in your comments on the draft decision regarding the timeline, you stated that you will perform additional analytical investigations and re-assess the read-across approach. ECHA notes that these proposed additional analytical investigations are not a request in the draft decision and therefore no additional time has been granted.

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. However, following your comments on the draft decision indicating a tonnage band downgrade, ECHA has taken into account the updated tonnage band (submission number [redacted] and date 17 April 2018), whereas no assessment of the updated registration has occurred. Based on the average production and/or import volumes for the three preceding calendar years, ECHA has changed the tonnage band as basis for the draft decision from [redacted] per year (submission number: [redacted] from 11 July 2017) to [redacted] per year (submission number: [redacted]).

The decision-making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

The compliance check was initiated on 13 September 2017.

ECHA notified you of the draft decision and invited you to provide comments. ECHA took into account your comments and your information about tonnage band downgrade. This has resulted in the removal of the following decision requests: Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat or rabbit), oral route; and Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route.

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. 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.