~~Confidential~~

Helsinki, 14 March 2022

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

Date of submission for the jointly submitted dossier subject to this decision
09 December 2021

Registered substance subject to this decision ("the Substance")
Substance name: Zinc bis(diethyldithiocarbamate)
EC number: 238-270-9

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 decision of 29 March 2016 ("the original decision") ECHA requested you to submit information by 5 April 2018 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 dossier specified in the header above, and concludes that

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

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

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit)

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

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

- Appendix A entitled "Reasons to request information required under Annex X of REACH", respectively.

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 have the duty under Articles 125 and 126 of Regulation No 1907/2006 to ensure that the requests in the original decision are enforced and complied with and, to that end, inter alia, to carry out checks and impose

effective, proportionate and dissuasive penalties[1].

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

[1] See paragraph 143 of the judgment of the European Court of Justice of 21 January 2021 in Case C-471/18 P Germany v Esso Raffinage.

[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 A: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study in a second species

You were requested to submit information derived with the registered substance for pre-natal developmental toxicity study (Annex X, 8.7.2.; test method: EU B.31./OECD 414) in rabbits, oral route.

In response, you provided results of a GLP compliant pre-natal developmental toxicity study (2017) according to OECD TG 414, in rabbits, via oral route (gavage), using the registered substance, as requested in the decision.

The doses used in the study were: 0, 2, 10 and 20 mg/kg bw/day in corn oil and was based on a dose range finding study (20 mg/kg bw/day caused reduction on food consumption and body weight gain, however no details were reported). The animals were exposed to the test material from gestation day (GD) 6 to 28.

For maternal toxicity, you considered a NOAEL of 20 mg/kg bw/day i.e. the high dose tested. No treatment related effects were noted in body weight, body weight gain, implantation sites, pre- and post-implantation losses, corpora lutea, mean ovary and uterus weights.

For developmental/embryotoxicity, you also considered a NOAEL of 20 mg/kg bw/day i.e. the high dose tested. There were no treatment related changes in number of litter size and weights. The malformations noted in the foetuses were of various type, not clearly increasing dose-dependently and hence treatment related effects could not be concluded.

We have reviewed this information and identified the following issue(s):

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 414. The key parameter(s) of this test guideline include that the highest dose level aims to induce some developmental and/or maternal toxicity.

In the provided study conducted according to OECD TG 414:

- The doses used were 0, 2, 10 and 20 mg/kg bw/day;
- You claimed the doses were selected based on results of preliminary performed study and in particular, on:
  - Lower body weight gain and food consumption (not statistically significant) observed in the high dose (20 mg/kg bw/day) group;
  - Your conclusion that the highest dose (20 mg/kg bw/day) used in a dose range finding study *'is expected to induce maternal toxicity in terms of effects on food consumption and body weight gain'* and therefore is to be used in the key study;
- You reported that no systemic toxicity (maternal and/or developmental) was noted in the key study.

First, the highest dose level in the study is not a limit dose and did not induce any systemic (maternal and/or developmental) toxicity.

Second, in the absence of substantiation of the claim that the doses were based on results of preliminary performed studies, you have not demonstrated that the highest dose level aimed to induce some systemic toxicity.

ECHA notes that on 18 May 2018, it sent you a separate communication (communication number: CCH-C-2114416426-53-01/F), requesting to provide a detailed information on the dose range finding study, as the highest dose used did not cause maternal toxicity, as required in the OECD TG 414.

You updated your registration dossier on 25 May, 8 August and 1 October 2019. However, you did not provide additional information on the dose range finding study. ECHA notes that the minor changes of the body weight alone cannot be considered as sufficient evidence on maternal toxicity.

Therefore, the dose level selection was too low. The study does not fulfil the key parameter set in OECD TG 414 and it is rejected.

In your comments to the draft decision you agree that only limited maternal toxicity is observed in the newly conducted OECD 414 study on zinc bis(diethyldithiocarbamate) (ZDEC) in rabbits and therefore the study does not meet the requirements of the OECD 414 test guideline.

You add that based on the information available on closely related structural analogues there is no evidence of developmental toxicity in either the rat or the rabbit for this group of substances. You propose that as no developmental effects were observed in the developmental toxicity study with ZDEC in rats, no developmental toxicity effects are expected to be found in a new OECD 414 study for ZDEC in rabbits. You further propose to apply a weight of evidence approach including the original OECD 414 study in rabbits performed with ZDEC and, according to Annex XI, Section 1.5, a read across from the structural analogues zinc bis (dibutyldithiocarbamate) (ZDBC) and zinc bis (dibenzyldithiocarbamate) (ZBEC). You consider that available information is considered to be sufficient to conclude that ZDEC does not have to be classified for developmental toxicity.

In support of your adaptation, you have provided the following sources of information:

In the technical dossier:

<u>With the Substance</u>:

(i) Pre-natal developmental toxicity study in rabbit via oral-gavage (according to OECD TG 414, GLP, 2017).

In your comments on the draft decision, as a part of the read-across justification document:

<u>With analogue substances</u>:

(ii) Summary of results of pre-natal developmental toxicity study in rabbit via diet (equivalent to OECD TG 414, GLP not specified, year not specified) with ZDBC, EC: 205-232-8;
(iii) Summary of results of pre-natal developmental toxicity study in rabbit via diet (equivalent to OECD TG 414, GLP, 2021) with ZBEC, EC: 238-778-0;
(iv) OECD QSAR Toolbox profile for source and target substances;
(v) A read-across justification document '*Justification for the read across approach according to Guidance on information requirements and chemical safety assessment (R.6.2.6)*'.

Based on the presented sources of information, you argue that the available data gives sufficient information to conlude on the pre-natal developmental toxicity because based on the information available on closely related structural analogues, there is no evidence of developmental toxicity in either the rat or the rabbit for this group of substances.

We have assessed this information and identified the following issue(s):

Weight of evidence

Annex XI, Section 1.2 states that there may be sufficient weight of evidence weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence adaptation.

However, your comments do not include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Reliability of provided information – evaluation of read-across

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

[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

In your comments to the draft decision, you have provided a read-across justification document.

You read-across between the structurally similar substances, zinc bis (dibutyldithiocarbamate) (ZDBC, EC: 205-232-8) and zinc bis (dibenzyldithiocarbamate) (ZBEC, EC: 238-778-0) as source substances and the Substance as target substance.

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

"Data from ZDBC is used as read-across source based on the toxicological profile and analogue structure with similar functional groups. The hypothesis for the relevant endpoint is that the structural difference in functional groups for ZDEC and ZDBC, ethyl groups versus butyl groups, have negligible influence on the hazard profile. Hence, the same (absence of) toxic effect for developmental toxicity is anticipated for both substances."

ECHA understands that you predict the properties of the Substance using 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.

Prediction issue: Bias of the prediction

In order to make an accurate prediction of toxicological properties all relevant information must be considered in the prediction. If not all information is considered in the read-across approach, bias can be introduced in the predictions which may result in an over/underestimation in the prediction (RAAF, 2017; Chapter 4.5.1.5.). Bias may be caused by incorrect/incomplete selection of source substance(s); or due to a particular selection of study(ies) performed on the source substance(s).

To justify the selection of source substances, you must provide documentation how the source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s), which other substances have been considered and why they have been discarded (RAAF, 2017, Chapter 4.4.1.5/4.5.1.5). If there are structural analogue(s) not used as source substances and data show significantly different results for the properties to be predicted without any justification for setting aside these different results, then the proposed prediction are considered biased.

You report information from the following source substances: zinc bis (dibutyldithiocarbamate) (ZDBC, EC: 205-232-8) and zinc bis (dibenzyldithiocarbamate) (ZBEC, EC: 238-778-0). As outlined above, you have provided the following justification on the selection of these substances used to predict the properties of the Substance:

"The target and source substance, all mono-constituents, are organometallic substances, containing a zinc bis(dithiocarbamate) backbone with four functional groups.The functional groups are ethyl, butyl and benzyl for ZDEC, ZDBC and ZBEC, respectively."

Based on the results of studies available on ZDEC and ZDBC, you conclude that the following NOAELs for the prenatal toxicity study in rabbits can be adopted from the rabbit study performed with ZDBC:

-Maternal NOAEL: 3330 ppm dietary equivalent to 101 mg/kg bw/day;

-Developmental NOAEL: 3330 ppm dietary equivalent to 101 mg/kg bw/day;

and that based on this information, it is concluded that ZDEC lacks any potential to interfere with development hence no additional OECD 414 study with ZDEC is necessary.

However for example the substance (zinc bis(dimethyldithiocarbamate), ziram; EC no 205-288-3) also has the following structure: a zinc bis(dithiocarbamate) backbone with four functional methyl groups.

Publicly available data from the disseminated registration dossier of ziram demonstrate the following effects:

In the pre-natal developmental toxicity study conducted with ziram in rabbit according to OECD TG 414 (GLP, oral-gavage, doses 3, 7.5, 15 mg/kg bw/day 1986), the NOAEL for maternal toxicity and developmental toxicity was 7.5 mg/kg bw per day, on the basis of decreased body-weight gain and food intake in the dams and post-implantation loss, reduced litter size, litter weight, fetal weight, and crown-rump length at 15 mg/kg bw per day. Ziram also induced diaphragm thinning in rat foetuses exposed to the substance *in utero (*pre-natal developmental toxicity study in rats (according to OECD TG 414, GLP, 1990) via oral-gavage at doses of 1, 4, 16, 64 mg /kg bw/day.

With a view to your selection of the source substances, you have not identified all relevant analogue substances that fall into the group that you identify and thus you have not taken into account the effects of these other substances in predicting the properties of your Substance, such as the abovementioned effects of ziram. Therefore, your predictions are biased and may underestimate the hazards of the Substance.

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 substances. 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.

Conclusion on your weight of evidence approach

As explained above, the provided information with source substances cannnot be reliably used for prediction of the properties of the Substance. Therefore it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 414 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Based on the above, the information you provided does not fulfil the information requirement and you are still required to provide a pre-natal developmental toxicity study in a second species, rabbits, oral route (Annex X, 8.7.2.; test method: EU B.31./OECD 414), with the 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[5].

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[6].

[5] https://echa.europa.eu/practical-guides
[6] 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 29 March 2016 ("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.

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.

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[7] 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)[8]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[9]

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[10]

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