ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 17 November 2017

Addressee: [redacted]

Decision number: CCH-D-2114375518-38-01/F
Substance name: Zinc bis(dibutyldithiocarbamate)
EC number: 205-232-8
CAS number: 136-23-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 06.11.2013
Registered tonnage band: >1000T

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. **Composition of each substance (Annex VI, Section 2.3.) of the registered substance;**
   - **Concentration range values**

2. **Description of the analytical methods (Annex VI, Section 2.3.7) of the registered substance;**
   - **Result of the quantification of the main constituent**

3. **Partition coefficient n-octanol/water (Annex VII, Section 7.8.; using an appropriate test method) with the registered substance;**

4. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2; test method: EU B.26/OECD TG 408) in rats with the registered substance with inclusion of analysis of thyroid hormones (T3, T4) and TSH levels;**

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

6. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2; test method: EU B.31/OECD TG 414) in a second species (rats/rabbits), oral route with the registered substance;**

7. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3; test method: EU B.56/OECD TG 443) in rats, oral route with the registered substance;**

   - **Ten weeks premating exposure duration for the parental (P0) generation;**

- **Dose level setting shall aim to induce some toxicity at the highest dose level;**
- **Cohort 1A (Reproductive toxicity);**
- **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
- **Cohorts 2A and 2B (developmental neurotoxicity).**

8. **Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1; test method: EU C.7/OECD TG 111) of the registered substance;**

9. **Sediment simulation testing (Annex IX, Section 9.2.1.4; test method: Aerobic and anaerobic transformation in aquatic sediment systems, EU C.24 / OECD TG 308) at a temperature of 12 °C with the registered substance;**

10. **Identification of degradation products (Annex IX, Section 9.2.3.) using appropriate test method; and**

11. **Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD TG 305) 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 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 **24 August 2021** except for the information requested under point 4 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **26 November 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point 7 after **25 February 2019**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

In order to ensure that potential hazardous properties of the substance are not underestimated, the information that is necessary to resolve the substance identification deficiencies below, must be available to you before identifying the test sample to be used for the testing requested in the present decision.

1. Composition of the substance (Annex VI, Section 2.3.)

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

Annex VI, section 2.3. of the REACH Regulation requires that each registration dossier contain sufficient information for establishing the composition of the registered substance and therefore its identity.

In that respect, according to chapter 4.3 of the Guidance for identification and naming of substances under REACH and CLP (Version: 1.3, February 2014), the Registrant shall note that, for well-defined substances, the following applies:

- Each main constituent (i.e. the constituent present at ≥80% for mono-constituent substance or each constituent present at ≥10% and 80% for multi-constituent substance) shall be identified and reported individually; and

- Each impurity present at ≥1% or relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually.

- For each constituent, the typical, minimum and maximum concentration levels shall be specified regardless of the substance type.

ECHA notes that you have provided the typical concentration values for the constituents of your substance specified in section 1.2 of the IUCLID dossier. However, the information on the concentration ranges (minimum and maximum concentration levels) for each constituent, have not been provided.

The minimum and maximum concentration levels of the constituents are necessary in order to understand the variability of the composition of the registered substance. Therefore, the registration does not contain sufficient and appropriate information for establishing the composition of the registered substance and therefore its identity.

Accordingly, you are required to specify the concentration range (minimum and maximum concentration levels) for each constituent of your substance.

The concentration range values must be representative for the registered substance as manufactured.

Regarding how to report the composition of the registered substance in IUCLID, the following applies: you shall report for each constituent of your substance the minimum, maximum and typical concentration, in the appropriate fields in Section 1.2 of the IUCLID dossier.

Further technical details on how to report the composition of well-defined substances in IUCLID are available in the Data Submission Manual – Part 18: How to report the substance identity in IUCLID 5 for registration under REACH (version: 2.0, July 2012) on the ECHA website.

ECHA notes that in your comments on the draft decision you agreed to provide the requested information.

2. Description of the analytical methods (Annex VI, Section 2.3.7.);

Annex VI, section 2.3.7 of the REACH Regulation requires that each registration dossier contains a sufficiently detailed description of the analytical method used for establishing the composition of the registered substance and therefore its identity. This information shall be sufficient to allow the method to be reproduced.

ECHA observes that you provided the description of an iodometric titration method to quantify the registered substance, however the results of the analysis are not reported.

Therefore, your dossier does not have sufficiently detailed information to verify the reported composition of the registered substance and therefore its identity.

Accordingly, you are required to provide the results of the titration method or to provide the description of any other suitable method used to establish the composition of the registered substance.

The description shall be sufficient for the methods to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained.

You shall ensure that the analytical data provided on the quantification of the substance is consistent with the composition and identity reported for the substance.

As for the reporting of the data in the registration dossier, the information should be attached in IUCLID section 1.4.

ECHA notes that in your comments on the draft decision you agreed to provide the requested information.

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PROPERTIES OF THE SUBSTANCE

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. Prior to documenting the reasons for requesting the individual information specified in Annexes VII to X, ECHA has analysed your arguments for adaptations based on on the grouping of substances and read-across approach.

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 the standard information requirements for

- Hydrolysis study (Annex VIII, Section 9.2.2.1)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Extended One-Generation Reproductive Toxicity Study (Annex X, Section 8.7.3.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and a property-specific context.

A. Description of the grouping and read-across approach

You propose to use grouping and read-across approach to adapt standard information requirements for the registered substance (zinc bis(dibutyldithio-carbamate, also referred as the target substance or ZDBC). Study results of a pre-natal developmental toxicity study obtained with the source substance zinc bis(diethyldithiocarbamate) (ZDEC) and study results of a two-generation reproductive toxicity and of a hydrolysis study obtained with the source substance zinc bis(dimethyldithio-carbamate) (ZDMC) are used to predict these properties for the registered substance.

Concerning the toxicological endpoints mentioned above, you claim that "*Human toxicological properties of both substances are expected to be governed by human toxicological properties of the respective cation and the organic moiety.*

As the substances have identical cations and structurally similar organic moieties with the same functionality, it is considered acceptable to derive the lacking data on human toxicological properties of ZDBC by read-across from ZDEC (ZDMC)". You further claimed that "*No significant difference in toxicological behaviour is expected to be seen between dibutyl- and diethylamine (dimethylamine) formed in the process of hydrolysis of dithiocarbamates, as their properties are primarily governed by the amine function and the substituents at the nitrogen atom are expected to have only a minor influence."*

Concerning hydrolysis, you claim that "*Dithiocarbamates all posses the same hydrolysable functional group*" and that "*Hydrolysis data is available for ZDMC only; for the structural analogues with Na+ as the cation the hydrolysis half-life seems to increase with decreasing size of the organic moieties present. Therefore, the hydrolysis half-life of ZDMC is taken into account as a worst-case assumption*".

ECHA understands this as the hypothesis under which you make predictions for the properties mentioned above.

B. Support of the grouping and read-across approach

You have provided read-across justifications as Appendices 4 and 5 in the CSR in the registration dossier. In these read-across justifications you provided the following arguments to support the read-across approach:

1. Target and source "*substances are zinc salts of dialkylcarbamodithioic acids, differing in the substituents at nitrogen atom of dithiocarbamate moieties (butyl vs. ethyl or methyl).*"

2. Physico-chemical properties of target and source substances are very similar. The substances are solids with negligible vapour pressure and very poorly soluble in water.

3. *"They are metabolized by a hydrolysis of a parent compound into the respective acid, which undergoes either a transformation to CS2, further oxidized into CO2, or a conjugation with glucuronic acid or GSH. No significant difference in toxicological behavior is expected to be seen between dibutyl- and diethylamine (dimethylamine) formed in the process of hydrolysis of dithiocarbamates, as their properties are primarily governed by the amine function and the substituents at the nitrogen atom are expected to have only a minor influence."*

4. Toxicokinetic study with the source substance ZDMC.

5. Hydrolysis study with the source substance ZDMC at pH 5, 7 and 9 at 25 °C.

6. *"As ZDEC (ZDMC) has a lower molecular weight in comparison to ZDBC, its absorption from the gut is likely to be at least as fast as ZDBC, if not faster. Therefore it is considered to be acceptable to derive data on prenatal developmental (resp. reproductive) toxicity of ZDBC by read-across from ZDEC (resp.ZDMC)."*

7. Data matrices of physico-chemical, environmental fate and toxicological properties of ZDBC and the structural analogues ZDEC and ZDMC including, among others, information about vapour pressure, water solubility, genotoxicity in vivo, skin and eye irritation, skin sensitization, acute toxicity via oral and dermal route and repeated dose toxicity, as well as prenatal developmental toxicity study with ZDEC and reproductive toxicity study with ZDMC.

ECHA notes that in your comments on the draft decision, you added an additional member to the zinc dithiocarbamates category: Zinc bis(dibenzyldithiocarbamate) (CAS no. 14726-36-4). However, you have submitted no information for this substance and this addition does not change the conclusions below.

C. 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:

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

In order to meet the provisions in Annex XI, 1.5 to predict physicochemical, toxicological and ecotoxicological properties 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.

As described under A. and B., you state that the properties of the target and source substances are governed by the (eco)toxicological profiles of the Zn2+ cation and the respective dithiocarbamate anions. Furthermore you expect that the toxicity of the organic anion is primarily governed by the amine function and that the substituents at the nitrogen have only minor influence.

In this regard ECHA notes:

a) The dissociation of the salt into the ions under aqueous conditions appears to be plausible. However, the salt as such cannot be disregarded when predictions are made since for the registered substance ZDBC and the source substance ZDEC no quantitative data are provided on the speed of this process under different pH conditions and no proof is provided that the salt is not taken up when exposure takes place. ECHA concludes that the salts may become systemically available, that the salts of the source and the registered substances have different structures and that the predictions do not take into account how this might influence the prediction.

b) The formation of Zn2+ and the formation of CS2 are demonstrated for one of the source substances (ZDMC). The formation of CS2 appears to be occurring via a number of intermediate steps (see (iii) b). However, it is not proven whether this formation is also occurring with the registered substance and the other source substance (ZDEC). If it is indeed occurring in all substances, it is not addressed whether the speed of the process is influenced by the butyl-substituents present in the registered substance versus the ethyl- or methyl-substituents in the source substances. ECHA concludes that the Zn2+ and CS2 appear to be plausible compounds formed from source and target substances. However, in the absence of quantitative data it is not clear how the amount/concentrations of these substances at different time points after administration may influence the toxicity profiles. In particular, information on the toxicity of Zn2+ and CS2 is missing in the dossier as well, so it is not possible for ECHA to verify any conclusions on these potential metabolites.

c) You explain that the hydrolysis of the organic acid results in CS2 and the dialkylamines (dimethylamine, diethylamine, or dibutylamine). There is no information on the toxicity profile of the dialkylamines in the dossier. Therefore your claim that the substituents on the nitrogen have only minor influence is not supported by data. ECHA concludes that the dissimilar dialkylamine structures and their potentially different toxicity have not been addressed in your explanations.

d) Finally, you have not shown how the substituents would influence the rate of hydrolysis, other than your mention that "*...hydrolysis half-life seems to increase with decreasing size of the organic moieties...*" , nor have you justified why "*the hydrolysis half-life of ZDMC is taken into account as a worst-case assumption*".

ECHA concludes that you have not addressed the obvious structural differences between the source substances and the target substance and did not explain why those differences would not lead to differences in the mode of action and in the toxicity profile and hydrolysis of target and source substances. The provided explanation is not considered as valid to establish the link between the structural similarity and the prediction. ECHA therefore considers that there is no adequate basis for predicting the properties of the registered substance from the source substances.

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

Annex XI, 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 substance involved are structural similar and are likely to have similar properties or follow a regular pattern. One important aspect in this regard is the data matrix comparing properties of source and target substances.

You provided limited data on properties of target and source substances in the data matrix. For repeated dose toxicity (combined toxicity/carcinogenicity study), you provided a LOAEL for the source substance ZDMC of 2.5 mg/kg bw/d based on severe toxic effects [degenerative/atrophic changes of the skeletal muscle (males), haemosiderin in the spleen (males), adipose replacement of exocrine pancreas (males), cortical degeneration of adrenals (males), prominent ultimobranchial cysts in the thyroid (females) and hyperplastic and erosive lesions of the stomach (males)]. ECHA observes that the source substance ZDMC has a STOT RE2 classification whereas the target substance does not. The repeated dose toxicity study on ZDEC has been conducted in 1953. Due to the limitations with regard to investigated parameters, quality assurance (not according to GLP, no other quality assurance mentioned) and reporting details this study does not meet the provisions of Annex XI 1.1.2 (2) and (4). Therefore this study is not considered to provide reliable information for a comparison of toxic effects observed in studies with repeated administration. For the target substance a 17-week non-GLP non-guideline study is provided which cannot be accepted as reliable source of information on repeated dose toxicity (see section 3 of this appendix).

ECHA concludes that the presented evidence in the data matrix does not support a similar or regular pattern of toxicity after repeated administration as a result of structural similarity. The similar or regular toxicity pattern is even less supported for pre-natal developmental effects or reproductive toxicity, since there is no information at all on these properties for the registered substance. Therefore ECHA considers that there is no adequate basis for predicting properties of the registered substance from the source substances.

(iii) Qualitative and quantitative exposure of the test organism to source and target substances and to their hydrolytic and/or metabolic products.

Annex XI, 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 comparison of absorption, distribution, metabolism and elimination of source and target substances to allow assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.
In this regard ECHA notes:

a) You stated that target and source substances are metabolized by a hydrolysis of the parent compound into the respective acid, which undergoes either a transformation to CS2 which is further oxidized into CO2, or a conjugation with glucuronic acid or GSH. Regarding absorption, you provided an argument as cited under section B. point 6 above. To support those claims, you provided a hydrolysis, and absorption, distribution, metabolism and excretion study with radioactively labelled source substance ZDMC in your registration dossier.

b) In the hydrolysis study, you reported that ZDMC was rapidly degraded in all three buffered solutions at pH 5, 7, and 9 with the respective half-lives calculated to be 624.32 seconds (10.4 minutes), 17.67 hours, and 6.31 days. You also reported that total of 11 degradates were observed in the entire study. You further stated that the major degradate in pH 5 and 7 buffered solutions was confirmed and identified as CS2, but characterization of the degradation products other than the major one was not pursued due to the extremely short half-life of ZDMC at either pH. Additionally, you reported that CS2 was also detected together with dimethyldithiocarbamic acid, carbon oxysulfide, isothiocyanic acid or thiocyanic acid, and N,N-dimethylformamide in the pH 9 buffered solution.

You reported that absorption was relatively slow with maximum concentrations of radioactivity being reached within 10 h at the low dose level and 24 h at the high dose level. You also reported that all tissues were exposed to the radiolabelled material within 2 h of administration with greatest concentrations of radioactivity at all time points were found in organs of metabolism and excretion (liver, lung, kidney), vascularised tissues (spleen, thyroid, adrenals), fat, blood and plasma. You claimed that excretion of radioactivity was rapid, the major proportion being excreted as volatiles in expired air within 24 h of administration; low levels of radioactivity were detected in all tissues at 168 h following dose administration and no accumulation of the source substance ZDMC seemed to occur. You identified the principal route of metabolism to be hydrolysis to form and exhale CS2, COS and CO2 (ca 51%). You also reported that the remaining dose was excreted in urine and faeces, with excretion essentially complete within 24 h. Metabolites found in urine included 2-dimethylamine-thiazolidine carboxylic acid and the S-glucuronide of dimethyldithiocarbamic acid and an unknown metabolite of apparent mass 326. Faeces contained thiram (ZDMC). ECHA acknowledges that the data on hydrolysis and ADME properties demonstrated that the source substance ZDMC is relatively slowly absorbed, systemically available to all tissues, and that it can be degraded or metabolised in many different compounds, of which not all could be characterized. ECHA notes that you have reported a use of radioactive labelling in that ADME study with ^{14}C presumably in the dithiocarbonyl group.

ECHA considers that this study does not provide information about the fate of the compound(s) arising from the source substance ZDMC after the ^{14}C containing group is eliminated from the compound. ECHA observes that you have characterized degradation products as dimethyldithiocarbamic acid, carbon oxysulfide, isothiocyanic acid or thiocyanic acid, and N,N-dimethylformamide in addition to CS2 at pH 9. Though the major hydrolysis degradation product of the source substance ZDMC was identified as CS2 at pH 5 and 7, the other degradation products could not be identified. Thus, ECHA considers that no supporting evidence was provided to which additional compounds the organism may be exposed due to (metabolic) degradation of the source substance ZDMC. ECHA further observes that no hydrolysis and toxicokinetic data is available in the dossier for the target substance ZDBC and source substance ZDEC to support your claim about hydrolysis and biotransformation of those substances.

Further, ECHA considers that you have not provided data to support your claim about absorption of the registered substance and source substance ZDEC. Though you expect that absorption of the source substances is likely to be at least as fast as in the target substance based on the molecular weights, ECHA is of the opinion that the molecular weight is not the only parameter which influences absorption. You did not consider other physico-chemical properties of the substances which may influence absorption rate, e.g., the lipophilicity of the organic moieties.

ECHA concludes that you did not address important aspects such as the toxicokinetics of the registered substance ZDBC and the source substance ZDEC, their metabolic fate / (bio)transformation and the resulting possible difference in the metabolic profile. From the information for ZDMC, ECHA concludes that the metabolic fate of ZDEC and ZDBC may be as complex as tentatively observed for ZDMC. However, no information is available for the principle routes or the speed of the metabolic processes. The time-concentration-profiles of the expected complex metabolic products is not known. Consequently, it is also not known which effects such metabolic products may have. Therefore, it is not possible to verify that the source substances and the target substance would show a similar or regular pattern of toxicity as a result of structural similarity. Therefore, ECHA considers that there is no adequate basis for predicting properties of the registered substance from the source substances.

D. Conclusion on the read-across approach

The adaptation of the standard information requirements for the endpoints pre-natal developmental toxicity study (Annex IX, Section 8.7.2.), extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) and hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.) in the technical dossier is based on the proposed read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

3. Partition coefficient n-octanol/water (Annex VII, Section 7.8.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation.

"Partition coefficient n-octanol/water" is a standard information requirement as laid down in Annex VII, Section 7.8 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 Section 2 of REACH Annex XI, with the following justification *"the study cannot be conducted, as the substance is virtually insoluble in water".*

ECHA considers that you did not provide enough information that demonstrates that it "is technically not possible to conduct the study as a consequence of the properties of the substance", as stated in Section 2 of REACH Annex XI. You did not provide any data or justification to prove that you could not use any of the methods given in ECHA *Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance* (version 6.0, July 2017) to measure "Partition coefficient n-octanol/water". Specifically, you have not demonstrated that it would be impossible to determine the substance concentration in either n-octanol or water.

Therefore, your adaptation of the information requirement cannot be accepted.

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 notes that in appendix A of the CSR document you have provided a calculated value for Log Kow of 7.04 (EpiSuite v4.0). You have however not provided any information on how that value was calculated. Therefore, it is not possible for ECHA to evaluate if the calculation provided would be sufficient to cover the information requirement.

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: Partition coefficient n-octanol/water. Guidance for determining appropriate test methods for the partition coefficient n octanol/water is available in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.1.8.3 (version 6.0, July 2017).

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 not provided any study record of a sub-chronic toxicity study (90-day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2, for the registered substance. You have provided for repeated dose toxicity:

> Gray, 1977, 17 weeks repeated dose toxicity study in rats via the oral route (feed) with the registered substance, key study, reliability 2 (according to your assessment), open literature study, purity of the test substance not specified, non-GLP, non-guideline.

ECHA notes that clinical observations, ophthalmological examinations or the tests of the functional observation battery have not been performed in this study. No results from histopathologic investigations are reported. Furthermore, only a limited number of the clinical biochemistry parameters have been measured. ECHA considers these limitations as major deviations from the OECD TG 408 requirements. In addition, the reporting of the study results does not allow an independent assessment of the findings, since tabular results and statistical analyses are not included. ECHA concludes that the presented information does not comply with the provisions for adaptation in Annex XI, Section 1.1.2. for the use of existing data, which have been obtained using methods not using GLP or test methods referred to in Article 13(3).

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.

The substance is a solid and is characterised as powder. You further characterise this powder as *"insoluble inhalable particles"* in your qualitative human exposure assessment. The CSR indicates that there are uses which lead to inhalation exposure [e.g. PROC 07, predicted Inhalation Exposure equal to [redacted] mg/m^3 (Table 91, p.125 in CSR)]. ECHA concludes that inhalation is an appropriate route of administration for the repeated dose toxicity study.

ECHA also notes that the substance is classified as respiratory irritant (STOT SE 3:H335 - May case respiratory irritation). You have conducted a qualitative assessment to document that the risks due to local irritation effects in the respiratory tract are controlled.

Even if the study presented by you for repeated dose toxicity (90-day) cannot be accepted as compliant with the requirements of Annex IX, Section 8.6.2, the reported results from this study indicate that systemic effects may dominate the toxicity profile of the registered substance, in particular effects on kidney and liver have been reported. Therefore, ECHA concludes that oral administration is also an appropriate route of administration for the repeated dose toxicity study.

In the current case, ECHA considers that an oral study provides more critical information to clarify possible systemic effects of the substance compared to a study conducted via inhalation. Therefore ECHA concludes that oral administration is the most appropriate route of administration. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method 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.

Following a proposal for amendment made by one of the Member State Competent Authorities, ECHA notes that there is available information derived from *in vitro* data on ZDBC and from the structurally analogue ZDMC (Ziram), that indicates concern for potential effect of ZDBC on thyroid. More specifically, thyroid was identified as one of the primary target organ for ZDMC (USEPA review Ziram, 2001). Although the read-across approach has been rejected,

ECHA aknowledges that Ziram is structurally similar to the registered substance, as you have also stated. Additionally, the *in vitro* positive and / or inconclusive results for ZDBC on thyroid hormone receptor activity (bio assay results published on pubchem, 2017) further supports the concern for potential effect of ZDBC on thyroid. Consequently, there is a concern for the potential effect of ZDBC on thyroid. As the OECD TG 408 protocol allows the inclusion of additional parameters "*if the known properties of the test substance may, or are suspected to, affect…specific hormones*", additional analysis of thyroid hormone measurement (T3, T4) and TSH shall be included in the study design of the test method EU B.26./OECD TG 408.

In your comments on the draft decision, you agreed with the opinion of ECHA on the data gap, but you considered that ECHA could consequently only ask for the submission of a testing proposal. You questioned ECHA's authority to request testing under compliance check evaluation, arguing that ECHA cannot in a compliance check circumvent the testing proposal procedure. Based on this view, you suggested to prepare and submit to ECHA a testing proposal for a 90-day repeated dose toxicity study. In your comments you further anticipate that this study, together with further information on ZDEC and ZBEC, should provide a solid basis for an even stronger read-across hypothesis.

Different from your interpretation, ECHA considers that 'bring[ing] the registration(s) into compliance' in the meaning of Article 41(3) REACH requires a concrete request for the standard information required under the REACH Annexes where a data gap has been identified. ECHA considers that testing proposal examinations and compliance checks are triggered by different needs, and certain timelines and safeguards may differ between the two processes. But both dossier evaluation processes ultimately follow the same decision-making process which results in a request for carrying out appropriate test(s) where this is required to meet the REACH information requirement under investigation.

As Annexes IX and X concern a number of vertebrate animal tests, the testing proposal examination process makes it mandatory for registrants to involve ECHA in order to ensure that such higher-tier testing is tailored to real information needs (Recital 63 of REACH).The testing proposal regime is to guarantee that ECHA is involved before testing is carried out, and that a decision on the proposed test is taken in close proximity to the registration deadline. For this purpose REACH foresees certain safeguards and timelines under Article 40 and 43 of the REACH Regulation.

By contrast, there is no particular deadline by which ECHA would need to check registrations for compliance according to Article 41 of the REACH Regulation, and the examination is not triggered by a specific proposal by a registrant. In any case, once ECHA initiates a compliance check, it will need to require tests where this is needed to bring the registration into compliance with the relevant information requirements.

Different from your interpretation of the REACH provisions, it is clear from the provisions on dossier evaluation (encompassing both testing proposal examinations and compliance checks) that ECHA decisions taken in accordance with the procedure laid down in Articles 50 and 51 of the REACH Regulation are to result in a request for generation of the standard information required under REACH, if a data gap was identified in the dossier evaluation process.

Requiring the submission of a testing proposal would not achieve compliance with the information requirement, but only further delay the generation of information. ECHA further notes that – through the commenting period – the Registrant has the opportunity to propose what he should in the first place have suggested in a testing proposal when he submitted his registration dossier. For all these reasons ECHA considers that the (draft) decision is not *ultra vires*. It also follows that ECHA would consider a possible future testing proposal to be inadmissible because the information requirement is already subject to this compliance check process.

Further, in your comments in the draft decision you request a phased approach and timing to be accepted by ECHA for the submission of the requested information. You outline a possible testing strategy for the category of zinc dithiocarbamates which includes combination of in vivo with in vitro studies to further improve the read-across justification for human toxicity.

ECHA notes that the present decision includes a paragraph explaining adaptation possibilities that is also (partly) applicable to the approach you propose in your comments: "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." ECHA, however, emphasises that any testing strategy or adaptation is your responsibility. With regard to your comment concerning the improvement of the read-across justification, ECHA refers you to above section C on the assessment of the proposed read-across.

In addition, the deadline in the draft decision allows sequential testing and therefore enables you to follow the phased approach as you proposes in your comments. The time limits set by ECHA are standard for all registrants in order to ensure equal treatment. Therefore, any case specific extension of a standard time limit is not possible since this would imply preferential treatment by ECHA.

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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats with inclusion of analysis of thyroid hormones (T3, T4) and TSH levels.

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 pre-natal developmental toxicity study [Nakaura, 1984] with the analogue substance zinc bis(diethyldithiocarbamate) (EC no 238-270-9).

However, as explained above in the section *'Grouping of substances and read-across approach'* of this decision, your adaptation of the information requirement cannot be accepted. 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.

According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with 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) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid (powder), ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision, you agreed with ECHA's findings and you indicated that you will prepare and submit to ECHA a testing proposal for a a pre-natal developmental toxicity study. In your comments you also aniticipate that this study, together with further information on ZDEC and ZBEC, should provide a solid basis for an even stronger read-across hypothesis. With regard to ECHA's authority and the inadmissibility of the testing proposal see ECHA's response to Registrant's comments under the request for sub-chronic toxicity (3. above).

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 (rats or rabbits) by the oral route.

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

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 1000 tonnes or more 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 does not contain information on a pre-natal developmental toxicity study with a second species and conducted with the registered substance. There is also no adaptation argument why a study with a second species would not be needed.

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 consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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

ECHA notes that in the comments to the draft decision you indicate that a PNDT study in second species it is not required by REACH at this juncture and imposing it would be disproportional and premature. You further note that:

- before performing the study you will consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI;
- you submit a testing proposal for the study only in case the read-across adaptation (supported by the results of 90 day toxicity study and PNDT study in 1st species with the registered substance) will not be considered appropriate.

ECHA understands that you do not agree that a pre-natal developmental toxicity study on a second species is a standard information requirement for a substance registered for 1000 tonnes or more per year. In this respect, ECHA emphasises that the pre-natal developmental toxicity study is an actual *standard* information requirement pursuant to Section 8.7.2., Annex X. This view was confirmed by the ECHA Board of Appeal in decision A-004-2012 of 10 October 2013 in which the Board of Appeal concluded that the provisions of the REACH Regulation, when read as a whole, mean that registrants manufacturing or importing substances at 1000 or more tonnes per year are required to perform a developmental toxicity study also on a second species, unless, as a result of the adaptations set out in the legislation, such a study is not necessary (see http://echa.europa.eu/about-us/who-we-are/board-of-appeal/decisions).

ECHA notes that according to column 2 of Annex X, Section 8.7. studies do not need to be conducted if substance is a known genotoxic carcinogen; or if the substance is known have adverse effects on fertility or to cause developmental toxicity (i.e. meeting the criteria for classification as Repro. 1A or 1B). ECHA concludes based on available information that the registered substance is not genotoxic and it does not meet the criteria for classification as Repro. 1A or 1B; therefore a pre-natal developmental study in a second species is required.

Further, ECHA points out that any improved adaptation based on Annex XI, section 1.5, of the REACH Regulation needs to meet the provisions of this section and has to address the shortcomings of the grouping and read-across proposal addressed in this decision.

With regard to ECHA's authority and the inadmissibility of the testing proposal, see ECHA's response to Registrant's comments under the request for sub-chronic toxicity (3. above).

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 rabbits or rats by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

7. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of Section 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Furthermore detailed guidance on study design and triggers is provided in in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017). Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of an extended one-generation reproductive toxicity study with the registered substance in the dossier that would meet the information requirement of Annex X, Section 8.7.3. You did also not provide as study record of a two-generation reproductive toxicity study (EU B.35, OECD TG 416) with the registered substance which was initiated before 13 March 2015 and which would be considerd appropriate to address this standard information requirement. Instead, 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 dietary two generation reproduction and developmental neurotoxicity study [[redacted] 1996] (similar to OECD TG 416) with the analogue substance zinc bis dimethyldithiocarbamate (ZDMC, EC no 205-288-3).

However, as explained above in the section *'Grouping of substances and read-across approach'* of this decision, your adaptation of the information requirement cannot be accepted. Hence, 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. Thus, an extended one-generation reproductive toxicity study according Annex X, section 8.7.3. is required. The following refers to the specifications of this required study.

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 6.0, July 2017). Ten weeks exposure duration is supported also by the expected lipophilicity (partition coefficient is not provided in the dossier, but open source information indicate that the estimated log Pow is equal to 7.04) of the substance to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) for the extended one-generation reproductive toxicity study are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that results obtained with the analogue substance zinc bis dimethyldithio-carbamate demonstrate developmental neurotoxicity effects in the offspring, such as increased motor activity and decreased mean peak startle response in a dietary two-generation reproduction and developmental neurotoxicity study ([redacted] 1996; in USEPA review Ziram/09/25/2001 available at:

http://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-034805_25-Sep-01_a.pdf). This information is not reported in the dossier. In this reference document also neurotoxic effects in adult animals (various species) are described for this substance.

Although the read-across to the analogue substance ZDMC in order to adapt the standard information requirement is rejected, ECHA considers this substance as a structural analogue in the meaning of column 2 of Section 8.7.3., Annex X (existing information on effects caused by structurally analogous substances to the substance being studied). As you have pointed out ZDBC and ZDMC are structurally similar zinc salts of dialkylcarbamodithioic acids, differing in the substituents at the nitrogen atom of dithiocarbamate moieties (butyl vs. methyl). ECHA considers therefore the information obtained with ZDMC as relevant to cause a particular concern for (developmental) neurotoxicity for the registered substance. Consequently this information is used to determine the design of the EOGRTS study.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* information on the structurally analogous substance zinc bis dimethyldithiocarbamate.

Species and route selection

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

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

ECHA notes that in the comments on the draft decision you indicated that a testing proposal for the requested test will be submitted only in case read-across adaptation (supported by newly derived data as the results of 90 day toxicity study) will not be considered appropriate.

ECHA points out that any improved justification for the use of an adaptation for the conduct of the extended one-generation reproductive toxicity study has to be submitted together with the results of the 90-day repeated dose toxicity study. Furthermore, any improved adaptation based on Annex XI, section 1.5, of the REACH Regulation needs to meet the provisions of this section and has to address the shortcomings of the grouping and read-across proposal addressed in this decision.

With regard to ECHA's authority and the inadmissibility of the testing proposal, see ECHA's response to Registrant's comments under the request for sub-chronic toxicity (3. above).

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: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohorts 2A and 2B (Developmental neurotoxicity)

Currently, the extension of Cohort 1B and the inclusion of Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request 3) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by **26 November 2018**. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **25 Februrary 2019** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **25 Februrary 2019**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision **24 August 2021**.

In your comments to the proposal for amendments, you have proposed to revise the text on sequential testing. In this proposal, you have not defined the timeline for evaluation of the results of the 90-day study. Instead, you have indicated that the results of the 90-day study will be evaluated by ECHA in consultation with the MSCAs once it is provided in the form of dossier update. In addition, you have indicated that "*ECHA will then decide if the updated dossier contains the correct proposal for an EOGRTS or a correct read across justification*". Furthermore, you mention that in case ECHA does not agree with your proposal, then a total of 6 months is required for "*a useful exchange of information among The Registrants, ECHA and the MSCAs [...], would meet the obligation to avoid unnecessary use of animals, and would, therefore, be beneficial for all parties concerned*".

ECHA would like to emphasise that the approach for sequential testing of the 90-day study and extended one-generation reproductive toxicity is agreed with the member states. With this regard, the 90-day study will be conducted before the extended one-generation reproductive toxicity study and the results shall be provided in the form of dossier update within 12 months from the date of the decision. Then, ECHA together with the member states will evaluate the results of the 90-day study within three months. If you have not received any communication from ECHA within 15 months from the date of the decision, then you can commence the extended one-generation reproductive toxicity study as specified in the decision. In case, there is a need to change the study design of the extended one-generation reproductive toxicity study, ECHA will inform you that a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation, to address the study design of the EOGRTS, will take place. In this case, you can only start the EOGRTS once you have received a new adopted decision from ECHA.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017)).
Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/ triggers must be documented.

8. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.)

"Hydrolysis as a function of pH" is a standard information requirement as laid down in Annex VIII, Section 9.2.2.1 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. In IUCLID section 5.1.2. in your technical dossier you provided the following justification for the adaptation: *"No hydrolysis study is available for zinc bis(dibutyldithiocarbamate). However, data from the structural analogue zinc bis(dimethyldithiocarbamate) will be used instead (for details see Reporting Format as attached to the respective IUCLID entry and CSR Appendix A.1). In a non-GLP, OECD 111 guideline study ([redacted] 1995) half-lives of zinc bis(dimethyldithiocarbamate) are measured in relation to the pH at 25 °C. The DT50 values are determined to be 10.4 min at pH 5, 17.7 h at pH 7 and 6.31 d at pH 9. The DT50 value of 17.7 h at pH 7 and 25 °C will be used in the assessment."*

However, as explained above in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted. Hence, 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. Thus, a hydrolysis study according to Section 9.2.2.1. of Annex VIII is required.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Hydrolysis as a function of pH (test method EU C.7. / OECD TG 111) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.2.2.1.

ECHA notes that in the comments to the draft decision you agreed to conduct the requested test. In additon, in your comments on the draft decision your indicate you intend to follow a phased approach by first generating data on the hydrolysis study on the registered substance and as far as possible and needed, identify the relevant metabolites. If the newly derived information indicates that further testing is required, you indicate that ECHA will decide.

ECHA agrees that undertaking hydrolysis testing initially could be done. Regarding ECHA providing further advice to you on your further testing, the current deadline of this decision allows for sequential testing for environmental fate and behaviour testing, thus you can decide on your testing strategy for the registered substance using the ECHA guidance mentioned below.

ECHA notes that guidance on how degradation/transformation products should be considered for various standard information requirements is given in different sections of ECHA's Guidance on Information Requirements and Chemical Safety assessment (for e.g. Chapter R.7b, Version 4.0, June 2017; Chapter R.11, Version 2.0, November 2014).

If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, to ensure compliance with this standard 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.

With regard to ECHA's authority see ECHA's response to Registrant's comments under the request for sub-chronic toxicity (3. above).

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: Hydrolysis as a function of pH (test method: EU C.7/OECD TG 111).

Notes for your consideration

ECHA would draw your attention to the OECD TG 111, paragraph 31 (Identification of hydrolysis products (Tier 3)), where it is specified that any major hydrolysis products, at least those representing ≥ 10% of the applied dose, should be identified by appropriate analytical method. In paragraph 35 (Treatment of results) of the test guideline it is further elaborated that the calculations of half-lives or DT_{50} values should also be applied to the hydrolysis products if appropriate.

9. Sediment simulation testing (Annex IX, Section 9.2.1.4.)

"Sediment simulation testing" is a standard information requirement as laid down in Annex IX, section 9.2.1.4. 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 using the following justification: "*In accordance with Column 2 of REACH Annex IX, degradation simulation testing in water and/or sediment does not need to be conducted as based on the available data risks are controlled and a refinement of the PECs with additional information on the degradation of the substance and its degradation products in water and sediment is therefore not required.*"

ECHA notes that in your PBT assessment reported in your technical dossier you conclude the following: "*Zinc dibutyldithiocarbamate is identified as potentially persistent. However, significant and substantial abiotic degradation occurs via hydrolysis. It is concluded that the major transformation products, dibutylamine and carbon disulfide, are not PBT nor vPvB substances, no further testing of degradation is required for the PBT/vPvB assessment.*"

Your justification for adaptation does not meet the criteria of either the specific adaptation rules of Column 2 of Annex IX, section 9.2 (substance not readily biodegradable, direct and indirect exposure of sediment is not unlikely), or the general adaptation rules of Annex XI. ECHA notes that according to your chemical safety assessment the refinement of the PECs with additional information on the degradation of the substance and its degradation products is indeed not required. However, in the PBT assessment available in your dossier/chemical safety report you conclude that "*substantial abiotic degradation occurs via hydrolysis*" and that "*the major transformation products, dibutylamine and carbon disulfide, are not PBT nor vPvB substances*". ECHA notes that the data provided for the hydrolytical degradation is solely based on the analogue substance ZDMC. As indicated above in Section '*Grouping of substances and read-across approach*' of this decision, the read-across is not acceptable and therefore does not fulfil the general adaptation rules of Annex XI.

Accordingly, there is currently a data gap for the hydrolysis endpoint because the adaptation for the sediment simulation testing endpoint cannot be accepted.

ECHA notes that based on the physico-chemical properties (Log Koc > 6, poorly water soluble) and the anticipated exposure based on the reported uses (adhesives and coatings, wide-dispersive uses), the water-sediment simulation test is considered appropriate to study the biodegradation.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Aerobic and anaerobic transformation in aquatic sediment systems (test method EU C.24. / OECD TG 308) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.4.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with Annex XIII of REACH regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "*the information used for the purposes of assessment of the PBT/vPvB properties shall be based on data obtained under relevant conditions*". The Guidance on information requirements and chemical safety assessment R.7b (version 4.0, June 2017) specifies that simulation tests "attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids [...], and a typical temperature that represents the particular environment". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-8 (version 3 February 2016) indicates 12°C (285K) as the average environmental temperature for the EU to be used in the chemical safety assessment. Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 308. Therefore, the test should be performed at the temperature of 12°C.

Simulation tests performed in sediment or in soil possibly imply the formation of non-extractable residues (NER). These residues (of the parent substance and/or transformation products) are bound to the soil or to the sediment particles. NERs may potentially be re-mobilised as parent substance or transformation product unless they are irreversibly bound or incorporated into the biomass. When reporting the non-extractable residues (NER) in your test results you should explain and scientifically justify the extraction procedure and solvent used obtaining a quantitative measure of NER.

In the comments on the draft decision you indicated that conduct of a sediment simulation test will be considered after assessment of the findings from the hydrolysis study on the registered substance and as far as possible and needed, identify the relevant metabolites ECHA emphasises that any testing strategy or adaptation is the Registrant's responsibility. ECHA notes that guidance on how degradation/transformation products should be considered for various standard information requirements is given in different sections of ECHA's Guidance on Information Requirements and Chemical Safety assessment (for e.g. Chapter R.7b, Version 4.0, June 2017; Chapter R.11, Version 2.0, November 2014).

If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, to ensure compliance with this standard 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.

ECHA notes your thorough analysis of these investigations of the substance's hydrolytic properties may allow you to conclude on the non-persistence of the registered substance. In the event that non-persistence of the substance in all relevant compartments can be shown and degradation products concluded not to be PBT/vPvBs the requested simulation testing might become unnecessary, as instructed by ECHA Guidance on information requirements and chemical safety assessment, Chapter R.11, Section R.11.4.1.1 (version 4.0, June 2017), *"If significant and substantial abiotic degradation has been confirmed and the hydrolysis transformation products have been assessed and concluded not to be PBT/vPvBs and it is certain that the fate properties of the substance do not attenuate the hydrolysis rate in sediment or soil, no further testing of degradation is required for the PBT/vPvB assessment"*.

With regard to ECHA's authority see ECHA's response to Registrant's comments under the request for sub-chronic toxicity (3. above).

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: Aerobic and anaerobic transformation in aquatic sediment systems (test method: EU C.24./OECD TG 308) at 12°C.

Notes for your consideration

Before conducting the requested sediment simulation test, you shall first update your chemical safety assessment. In particular, if you have decided first to conduct the test for hydrolytical degradation as function of pH requested in Section 7 of this decision, you shall then update the relevant parts of your chemical safety assessment (e.g. relevant PBT/vPvB assessment).

After the update of your chemical safety assessment, you shall consult the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11.4., section R.7.8.5 and Figure R.11-3 on PBT/vPvB assessment. The Guidance provides advice on the integrated testing strategy for the persistence assessment of the registered substance and its potential relevant constituents, impurities, additives and degradation/transformation products. Based on the outcome of the hydrolysis study requested in section 7 of this decision and the advice on the integrated testing strategy for the persistence assessment, you have to consider if further investigation on biotic degradation is required in order to make a definitive conclusion on the persistency in your PBT assessment. If you come to the conclusion that no further investigation on biotic degradation is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirements of Annex IX, 9.2.1.4.

9. Identification of degradation products (Annex IX, Section 9.2.3.)

"The identification of the degradation products" is a standard information requirement as laid down in Annex IX, section 9.2.3. of the REACH Regulation. Column 2 of Section 9.2.3. of Annex IX further states that the information does not need to be provided if the substance is readily biodegradable.

ECHA notes that the information on identification of the degradation products is not available in the registration dossier and no adaptation for this standard information requirement is provided.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Regarding the appropriate and suitable test method, the methods will have to be substance specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition degradation half-life, log Kow and potential toxicity of the metabolite may be investigated.

ECHA notes that in the comments to the draft decision you agreed to provide the requested information. In addition, in your comments on the draft decision your indicate you intend to follow a phased approach by first generating data on the hydrolysis study on the registered substance and as far as possible and needed, identify the relevant metabolites. If the newly derived information indicates that further testing is required, the registrant will undertake the identification of the degradation products using a suitable method.

ECHA notes that guidance on how degradation/transformation products should be considered for various standard information requirements is given in different sections of ECHA's Guidance on Information Requirements and Chemical Safety assessment (for e.g. Chapter R.7b, Version 4.0, June 2017; Chapter R.11, Version 3.0, June 2017).

If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, *to ensure compliance with this standard 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.*

ECHA notes your thorough analysis of these investigations of the substance's hydrolytic properties may allow you to conclude on the non-persistence of the registered substance. In the event that non-persistence of the substance in all relevant compartments can be shown and degradation products concluded not to be PBT/vPvBs the requested degradation testing might become unnecessary, as instructed by ECHA Guidance on information requirements and chemical safety assessment, Chapter R.11, Section R.11.4.1.1 (version 3.0, June 2017), *"If significant and substantial abiotic degradation has been confirmed and the hydrolysis transformation products have been assessed and concluded not to be PBT/vPvBs and it is certain that the fate properties of the substance do not attenuate the hydrolysis rate in sediment or soil, no further testing of degradation is required for the PBT/vPvB assessment"*.

With regard to ECHA's authority see ECHA's response to Registrant's comments under the request for sub-chronic toxicity (3. above).

Therefore, pursuant to Article 41(1)(a) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Identification of the degradation products using an appropriate test method, as explained above in this section.

Notes for your consideration

Before providing the above information you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R.7.9., Sections R.7.9.2.3 and R.7.9.4. These guidance documents explain that the data on degradation products is only required if information on the degradation products following primary degradation is required in order to complete the chemical safety assessment. Section R.7.9.4. further states that when substance is not fully degraded or mineralised, degradation products may be determined by chemical analysis.

10. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.)

"Bioaccumulation in aquatic species, preferably fish" is a standard information requirement as laid down in Annex IX, Section 9.3.2.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 using several justifications.

You have first used the following justification: *"In accordance with section 1 of REACH Annex XI, the study does not need to be conducted as in water, significant and substantial abiotic degradation of zinc bis(dibutyldithiocarbamate)occurs via hydrolysis and data is available for the degradation products that are potentially available for direct uptake in aquatic organisms."*

ECHA notes that you have proposed to adapt the standard information requirement of Annex IX, Section 9.3.2 by stating that the registered substance is not expected to bioaccumulate based on information on the bioaccumulation potential of its abiotic degradation products. ECHA assumes that the abiotic degradation products that you are referring to are the hydrolysis products. However, no hydrolysis data is submitted for the registered substance, only to a read across substance ZDMC. For the reasons stated above in Section *'Grouping of substances and read-across approach'* of this decision the read-across adaptation proposed for the hydrolysis endpoint is not acceptable. Hence ECHA considers that using hydrolysis as basis for adapting the standard information requirement of Annex IX, Section 9.3. is not a valid justification in this case (see also Section 7).

Additionally, in your technical IUCLID dossier section 5.3.1. and the CSR section 4.3.3 you have further sought to adapt the information requirement by a proposed read-across approach to tetrabenzylthiuramdisulphide (CAS no.10591-85-2) and zinc (mentioning the "Integrated Criteria Document Zinc" (ICDZ)) (Annex XI, 1.5.). You elaborated that:

"A bioconcentration test in fish is available for tetrabenzylthiuramdisulphide (CAS no.10591-85-2), which is a structural analogue lacking the central zinc ion and which has larger substituents at the nitrogen atom of dithiocarbamate moieties (benzyl vs. butyl). The experimental BCF of tetrabenzylthiuramdisulphide at steady state target concentrations of 0.5 and 5 µg/L were 118 ± 10 and 27 ± 3, respectively. As the benzyl groups are more lipophilic than the butyl groups, the experimental BCF values of tetrabenzylthiuramdisulphide can be seen as a worst-case assumption.

Based on the ICDZ data ([redacted]., 1993) on bioaccumulation of zinc in animals and on biomagnification (i. e. accumulation and transfer through the food chain), it is concluded that secondary poisoning is considered to be not relevant in the effect assessment of zinc. Major decision points for this conclusion are the following: 1) the accumulation of zinc, an essential element, is regulated in animals of several taxonomic groups, for example in molluscs, crustaceans, fish and mammals; 2) in mammals, one of the two target species for secondary poisoning, both the absorption of zinc from the diet and the excretion of zinc, are regulated. This allows mammals, within certain limits, to maintain their total body zinc level (whole body homeostasis) and to maintain physiologically required levels of zinc in their various tissues, both at low and high dietary zinc intakes. The results of field studies, in which relatively small differences were found in the zinc levels of small mammals from control and polluted sites, are in accordance with the homeostatic mechanism. These data indicate that the bioaccumulation potential of zinc in both herbivorous and carnivorous mammals will be low (EC, 2009).

In conclusion, data is available for the degradation products that are potentially available for direct uptake in aquatic organisms, and which do not indicate that zinc bis(dibutyldithiocarbamate) would be bioaccumulative. Therefore, a BCF test on zinc bis(dibutyldithiocarbamate) itself does not seem necessary."

ECHA notes that the substance tetrabenzylthiuramdisulphide (CAS No 10591-85-2) is not included in the group Dithiocarbamates on which you have provided analogue justification documents in Annexes of the CSR. ECHA also notes that you did not submit a robust study summary of the supporting study with the proposed read-across substance, which would allow ECHA to make an independent assessment of the study. You state that the BCF values obtained for this substance can be seen as a worst-case assumption as *"the benzyl groups are more lipophilic than the butyl groups"*.

ECHA considers that this statement alone cannot be used as a justification for indicating that the BCF values of tetrabenzylthiuramdisulphide do represent a worst case situation for the registered substance zinc bis(dibutyldithiocarbamate). Although benzyl groups are more lipophilic than butyl groups, you have not shown how these groups as part of a larger molecule or the potential abiotic and biotic degradation products would impact the bioaccumulation potential.

You have also used information on bioaccumulation and biomagnification of zinc as part of the justification to adapt this standard information requirement, although you did not submit any robust study summaries for this substance. ECHA considers it not applicable to use this information on its own to adapt the standard information of the registered substance zinc bis(dibutyldithiocarbamate), an organometallic substance, as you did not show how this reasoning applies to the whole molecule, including the organic part.

In conclusion, your justification for adaptation does not meet the criteria of either the specific adaptation rules of Column 2 of Annex IX, section 9.3.2. (the registered substance has a log Kow value of 7.04 and direct/indirect aquatic exposure is not unlikely), or the general adaptation rules of Annex XI. Therefore, the adaptations cannot be accepted.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7c* (version 3.0, June 2017) bioaccumulation in fish: aqueous and dietary exposure (test method EU C.13. / OECD TG 305) is the preferred test to cover the standard information requirement of Annex IX, Section 9.3.2.

ECHA Guidance defines further that results obtained from a test with aqueous exposure can be used directly for comparison with the B and vB criteria of Annex XIII of REACH Regulation and can be used for hazard classification and risk assessment. Comparing the results of a dietary study with the REACH Annex XIII B and vB criteria is more complex and has higher uncertainty. Therefore, the aqueous route of exposure is the preferred route and shall be used whenever technically feasible. If you decided to conduct the study using the dietary exposure route, you shall provide scientifically valid justification for your decision. You shall also attempt to estimate the corresponding BCF value from the dietary test data by using the approaches given in Annex 8 of the OECD 305 TG. In any case you shall report all data derived from the dietary test as listed in the OECD 305 TG.

In your comments on the draft decision you agreed with the principle of the request and indicated that you will decide on the need to conduct the study after the conduct of the study requested in sections 7 in the present decision.

Furthermore, in your comments you indicate that you intend to follow a phased approach by first generating data on the hydrolysis study on the registered substance and as far as possible and needed, identify the relevant metabolites. If the newly derived information indicates that further testing is required, the registrant will decide on the most suitable route of exposure to be used in the fish bioaccumulation study.

ECHA emphasises that any testing strategy or adaptation is the Registrant's responsibility.

ECHA notes that guidance on how degradation/transformation products should be considered for various standard information requirements is given in different sections of ECHA's Guidance on Information Requirements and Chemical Safety assessment (for e.g. Chapter R.7b, Version 4.0, June 2017; Chapter R.11, Version 2.0, November 2014).

If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, to ensure compliance with this standard 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.

As stated above in Section 8 and 9, a thorough analysis of these investigations of the substance's hydrolytic properties may allow you to conclude on the non-persistence of the registered substance. Furthermore before conducting testing, you are advised to consult the ECHA Guidance on the information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11. PBT/vPvB assessment, to consult the PBT assessment for Weight-of-Evidence determination and the integrated testing strategy for bioaccumulation assessment, in particular concerning relevant constituents, impurities, additives and degradation/transformation products. Also, you need to carefully consider the potential formation of stable degradation products with PBT/vPvB properties. Moreover, other than the PBT/vPvB assessment, other needs of the CSA (e.g. environmental hazard assessment, exposure assessment) for information on bioaccumulation of the substance has to be also considered by you.

With regard to ECHA's authority see ECHA's response to Registrant's comments under the request for sub-chronic toxicity (3. above).

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, Bioaccumulation in fish: aqueous or dietary bioaccumulation fish test (test method: OECD TG 305).

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 16 November 2015.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-55 written procedure and ECHA took the decision according to Article 51(6) 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 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.

3. 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.

4. Besides the data and cost sharing obligations pursuant to Article 53 of the REACH Regulation, please note that Article 11(1) of the REACH Regulation requires several registrants of the same substance to form a joint submission and submit data jointly. More precisely, the lead registrant acting with the agreement of the other assenting registrants shall submit the information listed in Article 11(1) on behalf of all registrants.