ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114321894-46-01/F Helsinki, 29 March 2016

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For zinc bis(diethyldithiocarbamate), CAS No 14324-55-1 (EC No 238-270-9), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for zinc bis(diethyldithiocarbamate), CAS No 14324-55-1 (EC No 238-270-9), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates submitted after 21 January 2016 the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The compliance check was initiated on 8 July 2013.

On 10 December 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 23 January 2014 ECHA received comments from the Registrant on the draft decision, concerning the information requirements of Annex I, Sections 1.4.1, 3.0.4., 3.3, 5 and 5; Annex VI, Sections 2.3.7. and 4; Annex VII, Section 7.8.; Annex VIII, Sections 9.2.2.1., 9.1.4.; Annex IX, Sections 7.16, 8.6.2., 9.1.6.1, 9.3.2. and 9.4.2.; and Annex X, Sections 8.7.2., 8.7.3, and 9.4.4 and 9.4.6.

On 16 April 2014 the Registrant updated his registration with the submission number [redacted].

The compliance check requirement to submit information of a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) has been removed from this draft decision due to the legislative amendments to the REACH Regulation regarding Annex X, Section 8.7.3. In light of this, ECHA Secretariat did not consider further the Registrant's comments and update concerning the information requirement of Annex X, Section 8.7.3. However, ECHA Secretariat did consider further the Registrant's comments and update concerning the information requirements of Annex I, Sections 1.4.1, 3.0.4., 3.3, 5 and 5, Annex VI, Sections 2.3.7. and 4, Annex VII, 7.8., Annex VIII, Sections 9.2.2.1. and 9.1.4.; Annex IX, Sections 7.16, 8.6.2., 9.1.6.1, 9.3.2. and 9.4.2.; and Annex X, Sections 8.7.2., 9.4.4 and 9.4.6. On the basis of all this information and change of scope, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 21 January 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vi) and (vii), 12(1)(e), 13 and Annexes VII, VIII, IX, X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

1. Dissociation constant (Annex IX, 7.16.; test method: OECD 112);
2. Hydrolysis as a function of pH (Annex VIII, 9.2.2.1.; test method: Hydrolysis as a function of pH, EU C.7./OECD 111);
3. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats;
4. Pre-natal developmental toxicity study (Annex X, 8.7.2.; test method: EU B.31./OECD 414) in rabbits, oral route;
5. Long-term toxicity testing on fish (Annex IX, 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD 210);
6. Bioaccumulation in aquatic species (Annex IX, 9.3.2.; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD 305;
7. Activated sludge respiration inhibition testing (Annex VIII, 9.1.4.; test method: Activated sludge, respiration inhibition test (carbon and ammonium oxidation), OECD 209);
8. Effects on terrestrial organisms:
   a. Long-term toxicity to terrestrial invertebrates (Annex X, 9.4.4.; test method: Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*) (test method: OECD 222), or Enchytraeid reproduction (test method: OECD 220), or Collembolan reproduction test in soil (test method: OECD 232));

b. Long-term toxicity testing on plants (Annex X, 9.4.6.); test method: Terrestrial plants, growth test (OECD 208), with at least six species tested (with as a minimum two monocotyledonous species and four dicotyledonous species) or test method: Soil Quality – Biological Methods – Chronic toxicity in higher plants (ISO 22030);
c. Effects on soil micro-organisms (Annex IX, 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216).

B. information related to chemical safety assessment and chemical safety report

Pursuant to Articles 41(1)(c), 41(3), 10(b), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report:

1. Revised derived no effect levels (DNELs) for workers and for the general population using the assessment factors recommended by ECHA and re-assessment of related risks or a full justification for not using the recommended assessment factors in DNEL derivation (Annex I, 1.4.1.);
2. Revised predicted no effects levels (PNECs) for Freshwater, Marine water, Sediment (marine water), Sediment (freshwater) and Soil using the assessment factors recommended by ECHA and re-assessment of related risks or a full justification for not using the recommended assessment factors in PNEC derivation (Annex I, sections 3.0.4. and 3.3.);
3. Revised exposure assessment and risk characterisation for the inhalation route (Annex I, 5 and 6).

C. Deadline for submitting the required information

Pursuant to Articles 41(4) and 22(2) of the REACH Regulation the Registrant shall submit to ECHA by **5 April 2018** an update of the registration dossier containing the information required by this decision[, including, where relevant, an update of the Chemical Safety Report]. The timeline has been set to allow for sequential testing as appropriate.

Note for consideration by the Registrant:

The Registrant 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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 the Member States.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier derived from the application of Annexes

VII to XI

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII, VIII, IX, and X of the REACH Regulation.

1. Dissociation constant (Annex IX, 7.16.)

"Dissociation constant" is a standard information requirement as laid down in Annex VII, Section 7.16. 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.

The technical dossier does not contain data to fulfil this information requirement. The Registrant sought to adapt the information requirement, but did not provide a sufficient justification. The registrant claims that "*In accordance with Section 1 of REACH Annex XI the study does not need to be conducted, as the substance does not contain functional groups which can undergo dissociation.*" This statement is not valid as the substance does contain a functional group which can undergo dissociation (e.g. amine functionality).

As explained above, the information available 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.

In his comments on the draft decision, the Registrant agreed to provide the requested information. In addition, the Registrant in his comments questioned ECHA´s authority to require testing under compliance check. The Registrant argues that ECHA cannot in a compliance check circumvent the testing proposal procedure, and argues that under compliance check ECHA may only require that a Registrant submits a testing proposal, if this information is missing.

ECHA considers that the Registrant's comment is based on a different interpretation of the REACH Regulation than that considered by ECHA. The testing proposal examination process for Annex IX and X information requirements is foreseen so that ECHA can ensure that such higher-tier testing is tailored to real information needs (Recital 63 of REACH).

Where a Registrant has neither adapted an Annex IX or X information requirement in a justified manner, nor complied with his obligation to make a testing proposal, the testing proposal examination process is not triggered. When ECHA identifies such incompliance, the compliance check process pursuant to Article 41 of the REACH Regulation is the appropriate tool to achieve the compliance of the registration with the applicable information requirements. Requiring the submission of a testing proposal would not achieve compliance with the information requirement (Article 43), 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. Therefore, the (draft) decision is not *ultra vires*.

In the updated dosser, the Registrant submitted testing proposals for dissociation constant (Annex IX, Section 7.16.) and Sub-chronic toxicity (90-days; Annex IX, Section 8.6.2.). On 22 August 2014 ECHA notified the Registrant about the inadmissible testing proposals contained within the update (Communication number: TPE-C-0000005392-76-01/F). ECHA acknowledges that the registrant has agreed with the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Dissociation constants in water (test method: OECD 112).

2. Hydrolysis as a function of pH (Annex VIII, 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.

The Registrant has not provided a hydrolysis as a function of pH study on the substance registered, instead he has sought to adapt the standard information requirement by submitting both an adaptation argument based on Column 2 of REACH Annex VIII, 9.2.2.1, and a read-across adaptation argument (Annex XI, 1.5.) by submitting a study with an analogue substance zinc bis(dimethyldithiocarbamate) (ZDMC; CAS No 137-30-4, EC No 205-288-3) as a key study.

a) Assessment of the adaptation based on Column 2 of REACH Annex VIII, 9.2.2.1

The adaptation in IUCLID section 5.2.1 provided by the Registrant is the following: *"In accordance with Column 2 of REACH Annex VIII, Hydrolysis testing (as required in section 9.2.2.1) does not need to be conducted as the substance is readily biodegradable."*

ECHA notes that the adaptation proposed by the Registrant based on the ready biodegradation of the substance is not valid since in the technical dossier under section '5.2.1. Ready biodegradation in water: screening tests' the Registrant has stated that the substance is not readily biodegradable. ECHA thus considers this adaptation as not valid.

b) Assessment of the adaptation based on a study with a read-across substance and read-across documentation

The study with the proposed analogue substance zinc bis(dimethyldithiocarbamate) (ZDMC; CAS No 137-30-4, EC No 205-288-3) is indicated as the key study. The Registrant reports in the technical dossier the robust study summary of the read-across substance.

Under the IUCLID endpoint summary of section 5.1.2 the Registrant has provided the following justification: *"No hydrolysis study is available for zinc bis(diethyldithiocarbamate). 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]) half-lives of zinc bis(dimethyldithiocarbamete) 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."*
In Annex A1 of the CSR the Registrant has provided justifications for using an analogue approach for environmental fate and environmental toxicity endpoints. The Registrant has followed the reporting format provided in ECHA Guidance R6 QSARs and grouping of chemicals. As a hypothesis for the analogue approach the Registrant states the following:

"This report addresses the analogue approach for the read-across of environmental endpoints of zinc bis(diethyldithiocarbamate) (ZDEC) with its structural analogues zinc bis(dibenzyldithiocarbamate) (ZBEC), zinc bis(dibutyldithiocarbamate) (ZDBC) and zinc bis(dimethyldithiocarbamate) (ZDMC). All four substances are zinc salts of dialkylcarbamodithioic acids, differing only in the substituents at the nitrogen atom of dithiocarbamate moieties (benzyl or different alkyl chain lengths). Comparison of available aquatic toxicity data among the four substances seems to indicate a decrease in toxicity with increasing size of the organic moieties present. Experimental data of ZDEC is lacking for the following environmental endpoints: Activated sludge respiration inhibition testing, Ready biodegradation, Hydrolysis as a function of pH". The Registrant further reports: *"Dithiocarbamates all posses the same hydrolysable functional group"* and *"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."* Under 'Degradation' in this document, the Registrant reports: *"All four substances hydrolyse in water. Data is available for ZBEC, ZDBC and ZDMC, with respect to chain lengths the dithiocarbamate moieties of ZDEC fall between ZDBC and ZDMC (ZDEC having ethyl vs. butyl and methyl for ZDBC and ZDMC, respectively). The structure of ZBEC is less similar to ZDEC as ZBEC has benzyl as the dithiocarbamate moieties and is therefore less suitable for read across."*

ECHA understands that the value for hydrolysis obtained with the analogue substance is used for predicting the same value for the registered substance. ECHA notes that the information provided by the Registrant in Annex A1 of the CSR does not support the analogue approach for hydrolysis and is conflicting. On one hand the Registrant reports that hydrolysis data are only available for ZDMC, on the other hand the Registrant reports that *"All four substances hydrolyse in water. Data is available for ZBEC, ZDBC and ZDMC, with respect to chain lengths the dithiocarbamate moieties of ZDEC fall between ZDBC and ZDMC..."* Further, the Registrant reports that the proposed read-across substance has the same hydrolysable functional group as the registered substance and indicates that *"for the structural analogues with Na+ as the cation the hydrolysis half-life seems to increase with decreasing size of the organic moieties present."* However, the Registrant did not provide any data to support this hypothesis. Furthermore, data provided in Annex A1 for other endpoints does not support read-across for hydrolysis. For instance, it is unclear how similar aquatic toxicity data would support the read-across for hydrolysis. Therefore, ECHA concludes that the adaptation based on the read-across approach is not acceptable.

ECHA further notes that the study submitted for the proposed analogue substance is a non GLP study conducted according to EPA Guideline Subdivision N 161-1 (Hydrolysis) and not OECD 111 which is the standard recommended by ECHA Guidance. According to the OECD 111 the hydrolysis result needs to be measured at 4 different pH values: at pH 1.2 (if physiologically important), and at pH 4.0, 7.0 and 9.0. In the study submitted only results for pH 5, 7 and 9 are submitted. Therefore, even if the read-across had been justified, the submitted study would not fulfil the conditions of Annex XI, 1.1.2 for being considered equivalent to the test methods referred to in Article 13(3) of the REACH Regulation.

As explained above, the information available 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 acknowledges that the Registrant in this comments agreed to conduct the requested test.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 111).

3. Sub-chronic toxicity study (90-day), oral route (Annex IX, 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

In the technical dossier the Registrant has provided a study record for a study published 1953 in *J. Pharmacol. Exp. Ther.* 109, 159-166. The Registrant rated this study with reliability 2 and flagged it as key study. According to the information provided, groups of 10 male and 10 female rats were administered diet containing zinc bis(diethyldithiocarbamate) at dose levels of 0, 500, 1000, 2500, 5000 and 10000 ppm for two years. The study determined a LOAEL of: 36 mg/kg bw/day (actual dose received) (male/female) based on hyperplasia of the thyroid gland in all dose groups.

Annex XI (1.1.2) provides the conditions which apply to data on human health and environmental properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3).
Data shall be considered to be equivalent to data generated by the corresponding test methods referred to in Article 13(3) if the following conditions are met:
(1) adequacy for the purpose of classification and labelling and/or risk assessment;
(2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

ECHA notes that the study from 1953 was neither conducted according to a test method referred to in Article 13 (3) nor according to GLP. Although condition (3) of Annex XI (1.1.2) is met by this study (duration is longer than a 90-day study), conditions (2) and (4) are not met. The OECD TG 408/EU B.26 for repeated dose 90-day oral toxicity study in rodents lists the key parameters to be investigated and reported in such a study. From those parameter food consumption and compound intake, ophthalmoscopic examination, clinical chemistry, urinalysis, neurobehaviour, and organ weights, are not reported in the study record. Furthermore the list of tissues investigated by histopathology in the 1953 study included heart, lung, thyroid, liver, stomach, spleen, kidney, adrenal, large and small intestine and gonads. OECD 408 states that additional tissues have to be investigated: histopathology of all gross lesions, brain (representative regions including cerebrum, cerebellum and medulla/pons), spinal cord (at three levels: cervical, mid-thoracic and lumbar), pituitary, parathyroid, thymus, oesophagus, salivary glands, pancreas, trachea and lungs (preserved by inflation with fixative and then immersion), aorta, uterus, accessory sex organs, female mammary gland, prostate, urinary bladder, lymph nodes (preferably one lymph node covering the route of administration and another one distant from the route of administration to cover systemic effects), peripheral nerve (sciatic or tibial) preferably in close proximity to the muscle, a section of bone marrow (and/or a fresh bone marrow aspirate), skin and eyes (if changes were observed during ophthalmological examinations). ECHA therefore concludes that the key parameters foreseen to be investigated in the OECD 408 study design are not covered by the study conducted in 1953. ECHA further notes that it is not clear whether any quality assurance has been performed nor is ECHA in a position to assess the results independently since statistical information has not been provided. Since conditions (2) and (4) of Annex XI 1.1.2 are not met , also condition (1) is not met

and the study alone is also not adequate for the purpose of classification and labelling and/or risk assessment.

As explained above, the information available 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.

In light of the physico-chemical properties of the substance (powder where [redacted]% of the particles are in the range of 10-100 µm) ECHA considers that testing by the oral route is most appropriate to determine the systemic toxicity of the registered substance.

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

In his comments on the draft decision, the Registrant agreed to provide the requested information. In addition, the Registrant in his comments questioned ECHA´s authority to require testing under compliance check. The Registrant argues that ECHA cannot in a compliance check circumvent the testing proposal procedure, and argues that under compliance check ECHA may only require that a Registrant submits a testing proposal; if this information is missing.

ECHA acknowledges that the Registrant in this comments agreed to conduct the requested test. In the updated dosser, the Registrant submitted a testing proposal Sub-chronic toxicity (90-days; Annex IX, Section 8.6.2.). 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 Dissociation constant (1. above).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 408) in rats.

4. Pre-natal developmental toxicity study (Annex X, 8.7.2.)

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 (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).
There is information available on this endpoint only for a pre-natal developmental toxicity study in a first species for the registered substance in the technical dossier. ECHA observes that the Registrant has neither provided a study record of a pre-natal developmental toxicity study in a second species in the dossier that would meet the information requirement of Annex X, Section 8.7.2. nor adapted this information requirement.

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

The test in the first species was carried out by testing a rodent species and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rabbit as a second species to be used.

In his comments to the draft decision the Registrant presented an adaptation based on grouping and read-across. This adaptation is assessed in the following sections.

a) 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 his comment and update of the technical dossier the Registrant have adopted this information requirement by providing a pre-natal developmental toxicity study in rabbits conducted with the analogue substance Zinc bis dimethyl dithiocarbamate, CAS No 137-30-4. A read-across justification document was provided in IUCLID section 13.

Annex XI, 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 the justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification.

b) Description of the grouping and read-across approach

The Registrant proposes to use grouping and read-across to adapt standard information requirements for the registered substance (Zinc bis(diethyldithiocarbamate), ZDEC). Study results of a pre-natal developmental toxicity study obtained with the source substance (Zinc bis dimethyl dithiocarbamate; ZDMC) are used to predict these properties for the registered substance. The Registrant further claim that "*No significant difference in toxicological behavior is expected to be seen between diethyl- and 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, the Registrant claims that "*Available toxicokinetic data indicate that the substances are metabolized via a hydrolysis of a parent compound, leading to the formation of CS_2 and the respective dialkylamine entering the subsequent metabolic pathways and thet "As ZDMC has a lower molecular weight in comparison to ZDEC, its absorption from the gut is likely to be at least as fast as ZDEC, if not faster.*"

ECHA understands this as the hypothesis under which the Registrant makes predictions for the properties mentioned above.

c) Support of the grouping and read-across approach

In the read-across justifications the Registrant has provided the following arguments to support the read-across approach:

i. Both the registered substance and the source substance *"are zinc salts of two dialkylcarbamodithioic acids, differing only in the substituents at nitrogen atom of dithiocarbamate moieties (ethyl vs. methyl)"*.
ii. Physico-chemical properties of target and source substances are very similar. Both substances are solids with negligible vapour pressure and very poorly soluble in water.
iii. *"Available toxicokinetic data indicate that the substances are metabolized via a hydrolysis of a parent compound, leading to the formation of CS_2 and the respective dialkylamine entering the subsequent metabolic pathways. No significant difference in toxicological behavior is expected to be seen between diethyl- and 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."*
iv. Toxicokinetic study with the source substance (ZDMC).
v. Hydrolysis study with the source substance (ZDMC) at pH 5, 7 and 9 at 25 °C.
vi. *"As ZDMC has a lower molecular weight in comparison to ZDEC, its absorption from the gut is likely to be at least as fast as ZDEC, if not faster."*
vii. Data matrix which show the available information on of physico-chemical and relevant toxicological properties of the registered substance (ZDEC) and the analogue substance (ZDMC) including, among others, information about vapour pressure, water solubility, genotoxicity, skin and eye irritation, skin sensitization, acute toxicity via oral and dermal route and repeated dose toxicity, as well as pre-natal developmental toxicity and reproductive toxicity study.

d) 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 and toxicological 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 sections 4. a) and 4. b) above, the Registrant states that the properties of the target and source substances are governed by the toxicological profiles of the Zn^{2+} cation and the respective dithiocarbamate anions. Furthermore the Registrant expects 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:

i. 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 (ZDEC) and the source substance (ZDMC) 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 substances and the registered substances have different

structures and that the predictions do not take into account how this might influence the prediction.

ii. The formation of Zn^{2+} and the formation of CS_2 are demonstrated for the source substance (ZDMC). The formation of CS_2 appears to be occurring via a number of intermediate steps (see section 4. d) (iii), point ii. However, it is not proven whether this formation is also occurring with the registered substance (ZDEC). If it is indeed occurring in both substances, it is not addressed whether the speed of the process is influenced by the ethyl-substituents present in the registered substance *v.* the methyl-substituent in the source substance. ECHA concludes that the Zn^{2+} and CS_2 appear to be plausible compounds formed from the 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 Zn^{2+} and CS_2 is missing in the dossier as well, so it is not possible for ECHA to verify any conclusions on these potential metabolites.

iii. The Registrant explains that the hydrolysis of the organic acid results in CS_2 and the dialkylamines (dimethylamine or diethylamine). There is no information on the toxicity profile of the dialkylamines in the dossier. Therefore, the 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 the explanations.

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

ECHA concludes that the obvious structural differences between the source substances and the target substance are not addressed and it is not explained 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.

The registrant has provided limited data on properties of target and source substances in the data matrix. For sub-chronic toxicity (90-days), the registrant has provided a LOAEL for the source substance (ZDMC) of 6.9-8.5 mg/kg bw/d based on thyroid effects. ECHA notes that, in addition, there is a combined toxicity/carcinogenicity study available on the source substance (ZDMC) this study is not included in the data matrix or the technical dossier. However, in this study there are severe toxic effects reported (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). The source substance (ZDME) has a harmonised classification as STOT RE2 and ECHA observes that the target substance does not have a STOT RE2 classification. The available sub-chronic toxicity (90-day) study on the registered substance (ZDEC) is considered by ECHA to be not adequate and reliable (see request 3. above). Therefore this study is not considered to provide reliable information for a comparison of toxic effects observed in studies with repeated administration.

With regard to pre-natal developmental toxicity there are studies in rats available on both the registered substance (ZDEC) and the source substance (ZDME). These studies provide maternal NOAELs of 125 mg/kg/day (*"Based on clinical signs of toxicity and mortality"*) and 4 mg/kg/day (*"based on increased water and decreased food consumption"*) for registered substance (ZDEC) and source substance (ZDME), respectively. The corresponding NOAELs for teratogenicity are 250 mg/kg/day (*"no adverse effects at the highest dose tested"*) and 4 mg/kg/day (*"based on reduced litter and mean foetal weight"*), respectively. ECHA notes that in pre-natal developmental toxicity studies generally no detailed investigations with regard to systemic toxicity are performed other than body weight and food intake measurements. ECHA notes that the NOAELs for maternal toxicity and teratogenicity differ significantly between source substance (ZDMC) and the registered substance (ZDEC). 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. 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 substance 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.

i. The registrant states that registered substance (ZDEC) and source substance (ZDMC) are metabolized by a hydrolysis of the parent compound into the respective acid, which undergoes either a transformation to CS_2 which is further oxidized into CO_2, or a conjugation with glucuronic acid or GSH. Regarding absorption, the Registrant has provided the argument as cited under section 4 b), point vi. above. To support those claims, the Registrant has provided a hydrolysis, and absorption, distribution, metabolism and excretion study with radioactively labelled source substance (ZDMC) in the technical dossier.

ii. In the hydrolysis study on the source substance (ZDMC), it is reported that it 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. It is also reported that total of 11 degradates were observed in the entire study. It is further stated that the major degradate in pH 5 and 7 buffered solutions was confirmed and identified as CS_2, 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, it is reported that CS_2 was also detected together with dimethyldithiocarbamic acid, carbon oxysulfide, isothiocyanic acid or thiocyanic acid, and N,N-dimethylformamide in the pH 9 buffered solution.

iii. In the toxicokinetic study conducted on the source substance (ZDMC), it is 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. It is 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. It is 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. The study identifies the principal route of metabolism to be hydrolysis to form and exhale CS_2, COS and CO_2 (ca [redacted]%). It is also reported that 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 (M1) and the S-glucuronide of dimethyldithiocarbamic acid and an unknown metabolite of apparent mass 326. Faeces contained thiram.*"

ECHA acknowledges that the data on hydrolysis and ADME properties demonstrates 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 the use of radioactive labelling in that ADME study is reported with ^{14}C presumably in the dithiocarbonyl group.

ECHA considers 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 degradation products are characterised as dimethyldithiocarbamic acid, carbon oxysulfide, isothiocyanic acid or thiocyanic acid, and N,N-dimethylformamide in addition to CS_2 at pH 9. Though the major hydrolysis degradation product of the source substance (ZDMC) was identified as CS_2 at pH 5 and 7, the other degradation products could not be identified. ECHA considers that thus 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) registered substance (ZDEC) to support the claim about hydrolysis and biotransformation of those substances.

Further ECHA considers that no dataare provided to support the claim about absorption of the registered substance (ZDEC) and source substance (ZDMC). Though it is expected 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. It is not considered how other physico-chemical properties of the substances may influence the absorption rate, *e.g.*, the lipophilicity of the organic moieties.

ECHA concludes that important aspects are not addressed such as the toxicokinetics of the registered substance (ZDEC) and the source substance (ZDMC), 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 the registered substance (ZDEC) may be as complex as tentatively observed for source substance (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.

(iv) Bias of the proposed prediction

Annex I section 1.1.4 requires "*...that the study or studies giving rise to the highest concern shall be used to establish the DNELs.;*" In the context of a read-across approach this has two aspects: the selection of the source substance and the selection of the source study.

ECHA notes that the registrant in his comments names nine carbamates as structural analogues. All substances "*have thiocarbamate as a common structure and consist of the following substances: Zinc dimethyldithiocarbamate (CAS no.137-30-4), Zinc diethyldithiocarbamate (CAS no. 14324-55-1), Zinc dibutyldithiocarbamate (CAS no. 136-23-2), Zinc dibenzyldithiocarbamate (CAS no. 14726-36-4), Sodium dimethyldithiocarbamate (CAS no. 128-04-1), Sodium diethyldithiocarbamate (CAS no. 148-18-5), Sodium dibutyldithiocarbamate (CAS no. 136-30-1), Sodium dibenzyldithiocarbamate (CAS no. 55310-46-8) and Tetramethylthiuramdisulfide (CAS no. 137-26-8).*" In contrast, the read-across approach used in the read-across justification document is an analoge approach between registered substance (ZDEC) and the source substance (ZDMC). No information is provided about the other analogue substances.

ECHA concludes that it is not possible to verify that the source substances were selected which are most appropriate and furthermore that the source studies were selected which are giving rise to the highest concern as required in Annex I, section 1.1.4.

e) Conclusion on the read-across approach

The adaptation of the standard information requirements for a pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.) 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.

In addition to the read-across adaptation above the Registrant argues that a pre-natal developmental toxicity study in a second species is not scientifically justified. The registrant brings forward three arguments: "*First, malformations may be due to genetic damage. Zinc bis(diethyldithiocarbamate) (ZDEC) is negative in all genotoxicity assays and has no alert for genotoxicity and thus malformations in offspring caused by genetic damage are not expected. Second, in the available prenatal developmental toxicity study in rats with ZDEC, no effects on development were observed up to the highest dose tested (250 mg/kg bw) while at that dose mortality was observed among the pregnant rats. Third, prenatal developmental toxicity studies in rats and rabbits with the structural analogue zinc bis(dimethyldithiocarbamate) (ZDMC) do not show that the rabbit is more sensitive compared to the rat. Based on these three arguments it can be concluded that a developmental toxicity in rabbit is not required.*"

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*). Furthermore, ECHA notes that the read-across adaptation proposed by the registrant has been rejected, see section 4 a) – e) above. ECHA concludes that the registered substance is -based on available information- not genotoxic, and that the available information on the registered substance do not meet the criteria for classification as *Repro. 1A or 1B*.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 414) in rabbits by the oral route.

5. Long-term toxicity testing on fish (Annex IX, 9.1.6.1.)

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant also submitted a read-across key study with Zinc bis(dimethyl dithiocarbamate), CAS No 137-30-4 in his updated dossier. In the summary section of IUCLID 6.1.2 the Registrant notes: "[...] *However, an early-life stage: reproduction study is available for the read-across substance zinc bis(dimethyldithiocarbamate). After additional testing (for more details see read-across justification) to strengthen the read-across approach and when the validity of the read-across hypothesis is confirmed, this study will be used for the risk assessment.*" This read-across study is addressed below.

In his comments on the draft decision, the Registrant:

1. agrees that the provided chronic fish early-life stage (FELS) toxicity test with the registered substance is not sufficient to completely fulfil the REACH information requirement.
2. questioned ECHA´s authority to require testing under compliance check, argues that ECHA cannot in a compliance check circumvent the testing proposal procedure, and argues that under compliance check ECHA may only require that a Registrant submits a testing proposal if this information is missing.
3. claims that , REACH does not impose any specific study to fulfil the information requirement of Section 9.1.6, but rather leaves a choice between three studies (fish early life-stage test; fish short-term toxicity test on embryo and sac-fry stages; fish, juvenile growth test)
4. states that REACH Annex IX column 2 provides that "*long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms.*" The Registrants further states that For the ZDEC dossier, additional short-term testing will be performed and, subsequently, a new CSA will be prepared. Therefore, the registrant suggests the following integrated testing strategy: "For aquatic toxicity, the registrant would like to have the opportunity to use a read-across approach with the structural analogues (see section B). For some substances in this category, tests will be performed to

fill in the missing data on of the three trophic levels (fish, algal or invertebrates) regarding acute effects as a result of exposure to the different substances, among them toxicity to aquatic plants (OECD 201).

A chemical safety assessment will then be performed with the new data obtained. If RCRs exceed 1, the need to perform further testing will be investigated and a proposal will be made which substances of the group will be tested, what kind of tests have to be performed, and for which substance read-across can be used.

The Registrant concludes that ECHA's request for a long-term toxicity test on fish is premature.

ECHA notes that, in addition to the comments, the Registrant has also updated the dossier providing an updated read-across justification document.

ECHA's response to the issues raised in the registrants comment is outlined below.

1. ECHA acknowledges that the Registrant agrees that the provided data on the chronic fish early-life stage (FELS) toxicity test are not sufficient to completely fulfil the REACH information requirement agreed to conduct a new study.
2. 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 Dissociation constant (1. above).
3. ECHA considers that for the endpoint of long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6.1, the FELS toxicity test according to OECD 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA *Guidance on information requirements and chemical safety assessment* (version 1.2., November 2012), Chapter R7b, Figure R.7.8-4 page 26). The test method OECD 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance R7b, version 2.0, November 2014, p. 29). For these reasons, ECHA considers the FELS toxicity test using the test method OECD 210 as appropriate and suitable.
    - OECD TG 212:
      The guidance mentions: "*It [OECD 212] is considerably shorter, and hence less expensive, than the FELS toxicity test but it is also considered less sensitive.*"
      Importantly, paragraphs 2-4 of the OECD testing guideline mention: "*2. This guideline is intended to define lethal, and to a limited extent, sublethal effects of chemicals on the specific stages and species tested*
      3. This Guideline does not replace Guideline 210 but it would provide useful information in that it could (a) form a bridge between lethal and sublethal tests, (b) be used as a screening test for either a Full Early Life Stage test (Guideline 210) or for chronic toxicity and (c) be used for testing species where husbandry techniques are not sufficiently advanced to cover the period of change from endogenous to exogenous feeding.
      4. It should be borne in mind that only tests incorporating all stages of the life-cycle of fish are generally liable to give an accurate estimate of the chronic toxicity of chemicals to fish, and that any reduced exposure with respect to life stages may reduce the sensitivity and thus underestimate the chronic toxicity.

It is therefore expected that the embryo and sac-fry test would be less sensitive than the Full Early Life Stage test (Guideline 210), particularly with respect to chemicals with high lipophilicity (log Pow > 4) and chemicals with a specific mode of toxic action."

- OECD TG 215:
  The guidance mentions: "*Although it is considered to be of insufficient duration to examine all the sensitive points in the fish life-cycle, it provides a shorter and less expensive option to the FELS test for substances of log Kow<5.*"

From the above it is clear that ECHA, in requesting the information requirement of Section 9.1.6. to be fulfilled with the OECD 210 testing guideline, is ensuring that vertebrate testing (as a last resort) is optimally and most efficiently used: if vertebrate testing is deemed necessary, the most sensitive guideline providing full coverage for the information requirement of long-term toxicity testing on fish is requested, *in casu* OECD testing guideline 210. This is especially true for newly conducted studies with fish. ECHA finally notes that the OECD 210 guideline has been updated in 2013 to reflect experience in using the test and recommendations from an OECD workshop on fish toxicity testing, held in September 2010 and is therefore a more up to date guideline than the OECD 212 (dating 1998) and 215 (dating 2000).

4. Read-across and testing strategy.
   - Adaptation provided by the Registrant – 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 his comments and update of the technical dossier the Registrant has adapted this information requirement by providing a key study conducted with the analogue substance Zinc bis(dimethyl dithiocarbamate), CAS No 137-30-4. A read-across justification document is provided in IUCLID section 13.
     Annex XI, 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 the justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification.
   - Description of the grouping and read-across approach:
     The registrant proposes a one-to-one read-across from the source substance zinc bis(dimethyldithiocarbamate) (ZDMC) to the target substance zinc bis(diethyldithiocarbamate) (ZDEC), supported by a category of 4 substances: ZDEC, ZDMC, zinc bis(dibenzyldithiocarbamate) (ZBEC), and zinc bis(dibutyldithiocarbamate) (ZDBC). The registrant considers the substances structurally similar "*dialkylcarbamodithioic acids, differing only in the substituents at the nitrogen atom of dithiocarbamate moieties*". Based on the data available for the category members, the registrant identifies a trend for ecotoxicity with lower toxicity for substances with a higher logKow. Therefore, the registrant considers ZDMC a worst-case read-across substance for ZDEC. The Registrant concludes for the category members that "*physico-chemical properties of the four substances are either similar or follow a logical trend.*

[...] *Hydrolysis tests for ZDEC, ZBEC, and ZDBC will be performed, but all dithiocarbamates possess the same hydrolysable functional group. Therefore it is expected that all substances will hydrolyse similarly.* [...] *In general it can be observed that aquatic toxicity decreases with increasing log kow value* [...] *all data indicate that with increasing log Kow levels toxicity decreases i.e. results obtained from studies with ZDMC can be considered worst-case for the risk assessment of ZDEC, ZBEC, and ZDBC."*
In his hypothesis for the category approach, the Registrant concludes: "*Comparison of available aquatic toxicity data among the four substances seems to indicate a decrease in toxicity with increasing log Kow levels."*

ECHA understands that the Registrant wants to read-across chronic toxicity to fish and ready biodegradability from ZDMC to ZDEC on the basis of a trend (decreasing toxicity with increasing logKow) and that ZDMC is considered a worst-case ZDEC.

- Support of the grouping and read-across submitted by the Registrant:
  In the read-across justifications the Registrant has provided the following arguments to support the read-across approach:
  i. The four category members "*are zinc salts of dialkylcarbamodithioic acids, differing only in the substituents at the nitrogen atom of dithiocarbamate moieties (benzyl or different alkyl chain lengths).*"
  ii. "*Physico-chemical properties of the four substances are either similar or follow a logical trend. The substances are all solids with negligible vapour pressure and are all poorly soluble in water (around 1 mg/l). The log kow values increases from ZDMC< ZDEC<ZBEC<ZDBC. Hydrolysis tests for ZDEC, ZBEC, and ZDBC will be performed, but all dithiocarbamates possess the same hydrolysable functional group. Therefore it is expected that all substances will hydrolyse similarly.*"
  iii. Short-term and long-term aquatic toxicity data on the category members. From these data, the Registrant concludes "*all data indicate that with increasing log Kow levels toxicity decreases i.e. results obtained from studies with ZDMC can be considered worst-case for the risk assessment of ZDEC, ZBEC, and ZDBC.*"
  iv. A data matrix showing the available information on of physico-chemical and ecotoxicological properties of the registered substance (ZDEC), the analogue substance (ZDMC) and the 2 other group members (ZBEC and ZDBC).
- ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.:
  i. Explanation on why and how the structural features allow predictions.
  In order to meet the provisions in Annex XI 1.5 to predict physicochemical and toxicological 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.

  Concerning the hypothesis ECHA notes that the hypothesis section in the Registrant's read-across justification document does not include a

real hypothesis. The Registrant did not provide a mechanistic explanation (including for instance the presumed mode of action) for the observed (trend in) toxicity of the group members. Importantly, category members are used as pesticides which very likely have a specific mode of action. From the human health read-across document it can be derived that metabolites can be important in the toxicity profile of the substance. In analogy, for substances that are used as pesticides, likely to have a specific mode of action, hydrolysis/degradation/metabolisation products might be important. The Registrant has made no attempt to explain any of the observed toxicity or trends referring to mode of action and/or hydrolysis/degradation/metabolisation products. In this respect, ECHA further notes that the trend observed by the Registrant (decreasing toxicity with increasing logKow) is the opposite of trends observed for many classes of chemicals.

ii. Support of a similar or regular pattern as a result of structural similarity.
The trend described by the Registrant is opposite of trends observed for many chemical classes where – between certain limits of logKow – generally toxicity increases with increasing logKow. The trend observed by the Registrant is not confirmed by all fish toxicity data. The registrant did not explain the trends or the deviations from this trend. This is partly due to the lack of (mechanistic) hypothesis (e.g. mode of action, including hydrolysis, dissociation, metabolisation and/or degradation products). The contribution to ecotoxicity of hydrolysis, dissociation, degradation products and metabolites of the different group members and of ZDMC and ZDEC in particular can affect the trend in ecotoxicological properties. ECHA notes that for important physico-chemical and fate parameters data on the group members is limited: experimental data on logKow and hydrolysis is currently only available for ZDMC, experimental data on water solubility is only available for ZDMC and ZDEC. The category covers a very large range physico-chemical parameters (e.g. logKow, water solubility), but there are only 4 group members with limited data on a number of important physico-chemical parameters. This makes a sound explanation of the trends difficult. Therefore, ECHA concludes that the Registrant did not show how the read-across from ZDMC to ZDEC is a worst-case and did not show how the information from the category members would support the read-across.

- Conclusion on the read-across approach:
The adaptation of the standard information requirements long-term toxicity testing on fish (Annex IX, Section 9.1.6.) 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 for environmental and fate endpoints in the technical dossier that are based on Annex XI, 1.5.

The Registrant also provided a supporting study which is described by the Registrant as *"Non-GLP, guideline study, available as unpublished report, minor restrictions in design and/or reporting but otherwise adequate for assessment."* Further, the study is described by the Registrant as being performed according to or equivalent to the OECD 210 guideline. The Registrant also reports *"The medium was renewed after two or three days, only eggs were exposed to the test medium."*

ECHA observes shortcomings with this study and important differences from the OECD 210 guideline:

- the total test duration was only 11 days instead of the recommended 30 days post-hatch;
- only eggs were exposed;
- there was no analytical monitoring in the study;
- semi-static conditions were used while the OECD 210 guideline prefers flow-through conditions;
- less than 60 eggs per concentration were used.

ECHA also notes that the robust study summary reported in IUCLID section 6.1.2. does not contain details in the 'Results and discussions', 'Overall remarks', 'attachments', and 'Applicant's summary and conclusion' section. For instance, no information is provided on observations (i.a. control survival of fertilised eggs, hatching success, post-hatch survival, abnormal appearance and behaviour, individual weights), dose-response relationships, (i.a. description of statistical analysis). Such data should be included in a robust study summary.

Therefore, ECHA decides that this study is not sufficient to fulfil the information requirement of Annex IX, Section 9.1.6. of the REACH Regulation.

ECHA further notes that the NOEC of the reported 11 day fish study is similar to the NOEC in the long-term *Daphnia* study and therefore the NOEC for fish would likely be lower if a full-length OECD 210 study had been conducted.

In the testing strategy proposed by the Registrant in his comments, he states: *"[...] If RCRs exceed 1, the need to perform further testing will be investigated and [...]"* ECHA notes that *"based on the CSA"* as mentioned in Annex IX, 9.1.6, column 2 is not limited to the RCR only. Other considerations (specific mode of action, high sensitivity of a particular group of organisms...) can play a role in this assessment.

As explained above, both the key study with the read-across substance and the supporting study with the registered study in the technical dossier do not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Regarding the long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6.1, ECHA considers that the FELS toxicity test according to OECD TG 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b, Figure R.7.8-4). The test method OECD TG 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance Chapter R7b, version 2.0, November 2014). For these reasons, ECHA considers the FELS toxicity test using the test method OECD TG 210 as most appropriate and suitable.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision:
Fish, early-life stage (FELS) toxicity test (test method: OECD 210).

Notes for consideration by the Registrant:

According to ECHA Guidance on information requirements and chemical safety assessment (version 1.2, November 2012), Chapter R7b, Figure R.7.8-4 page 56, if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. The Guidance also sets out an integrated testing strategy, i.e. that – if a chronic study on algae is available – the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and an applied assessment factor of 50 no risks are indicated, no long-term fish testing may need to be conducted. However, if a risk is indicated when applying an assessment factor of 50, long-term fish testing may need to be conducted. However, in the present case and as explained below in section III.D PNEC freshwater, no long-term data for algae are available. Therefore, in line with Table R.10-4 of Guidance on information requirements and chemical safety assessment, Chapter R.10: Characterisation of dose [concentration]-response for environment (version May 2008) an assessment factor of 100 should be applied to the results of the long-term *Daphnia* study. If based on the results of the long-term *Daphnia* study and an applied assessment factor of 100 no risks are indicated, no long-term fish testing may need to be conducted. However, if a risk is indicated when applying an assessment factor of 100, long-term fish testing may need to be conducted.

The Registrant has not included an adaptation argument based on the integrated testing strategy set out in the Guidance in his registration dossier. For such an adaptation to be justified, the CSR would also need to be consistent with the arguments raised in the adaptation argument.

5. Bioaccumulation in aquatic species (Annex IX, 9.3.2.)

"Bioaccumulation in aquatic species" 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.

The Registrant has waived testing bioaccumulation in aquatic species using the following justification in the robust study summary of IUCLID 5.3.1: "*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(diethyldithiocarbamate) occurs via hydrolysis and data is available for the degradation products that are potentially available for direct uptake in aquatic organisms.*"

ECHA notes that the Registrant has proposed to adapt the standard information requirement of Annex IX, Section 9.3.2 by stating that the substance registered is not expected to bioaccumulate based on information on the bioaccumulation potential of its abiotic degradation products. ECHA assumes that the abiotic degradation products the Registrant refers to are the hydrolysis products. However, no hydrolysis data is submitted for the registered substance, only for a read across substance zinc bis(dimethyldithiocarbamate) (CAS no.137-30-4). For the reasons stated under section III.B.3 above 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 the endpoint summary of IUCLID 5.3.1 and the CSR section 4.3.3 the Registrant has 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.). He 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]) 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(diethyldithiocarbamate) would be bioaccumulative. Therefore, a BCF test on zinc bis(diethyldithiocarbamate) 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 the Registrant has provided analogue justification documents in Annexes of the CSR. ECHA also notes that the Registrant did not submit a robust study summary of the supporting study with the proposed read-across substance. The Registrant states that the BCF values obtained for this substance can be seen as a worst-case assumption as the *"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(diethyldithiocarbamate). Although benzyl groups are more lipophilic than butyl groups, the Registrant has not shown how these groups *as part of a larger molecule* or the potential abiotic and biotic degradation products would impact the bioaccumulation potential.

The Registrant has also used information on bioaccumulation and biomagnification of zinc as part of the justification to adapt this standard information requirement, although he 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(diethyldithiocarbamate), an organometallic substance, as the Registrant did not show how this reasoning applies to the whole molecule, including the organic part.

The justification for waiving provided by the Registrant does not meet the criteria of either the specific adaptation rules of Column 2 of Annex IX, section 9.3.2., or the general adaptation rules of Annex XI. Therefore, the adaptations cannot be accepted.

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

The ECHA Guidance on information requirement and chemical safety assessment Chapter R7C (version 1.1., November 2012) recommends the bioaccumulation test on fish to be carried out using dietary exposure for certain types of substances due to their specific physical chemical properties (e.g. low water solubility, Log Kow > 6). As also a study for Partitioning coefficient n-octanol/water is requested in this decision (section 2 2.1) no accepted value for Log Kow is currently present in the technical dossier. Therefore ECHA is not in the position to decide on the most suitable route of exposure to be used in the fish bioaccumulation study. The Registrant is to decide on the route of exposure once the results of the Partitioning coefficient n-octanol/water requested under section II.B.1. of the present decision are available.

In his comments the registrant states that he intends to follow a phased approach by first generating data on the hydrolysis of ZDEC and the break-down products. If the newly derived information indicates that testing is required, the registrant will decide on the most suitable route of exposure to be used in the fish bioaccumulation study and a testing proposal for bioaccumulation in fish: aqueous and dietary exposure (test method: OECD 305) will be submitted.

ECHA notes that, in addition to the comments, the Registrant has also updated the dossier reflecting the proposed approach in the endpoint summary (section 5.3.1) and in the CSR

(section 4.3.3). The Registrant added 2 sentences to the IUCLID section 5.3.1: "In addition, an experimental study (OECD 111) is planned for zinc diethyldithiocarbamate (14324-55-1) which will replace the hydrolysis study with the read-across substance ZDMC. Based on the newly derived information the registrant will re-evaluate whether a BCF test on zinc bis(diethyldithiocarbamate) itself is still not necessary." The Registrant has not included new information/read-across justifications in the dossier on the analogue substance tetrabenzylthiuramdisulphide (CAS no.10591-85-2).

ECHA agrees that undertaking hydrolysis testing initially could be done. However, as compliant hydrolysis information is currently missing from the dossier, the request for bioaccumulation still remains.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Bioaccumulation in fish: aqueous and dietary exposure (test method OECD 305).

6. Activated sludge respiration inhibition testing (Annex VIII, 9.1.4.)

"Activated sludge respiration inhibition testing" is a standard information requirement as laid down in Annex VIII, Section 9.1.4 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.

The Registrant has not provided an activated sludge respiration inhibition testing study on the substance registered, instead he sought to adapt the information requirement by a proposed read-across argument (Annex XI, 1.5.). He submitted a robust study summary on an analogue substance zinc bis(dibutyldithiocarbamate) (ZDBC; CAS No 136-23-2, EC No 205-232-8) marked as the key study. Furthermore, under the Endpoint summary of section 5.1.2. in IUCLID the Registrant has provided the following justification: *"No respiration inhibition tests with activated sludge are available for zinc bis(diethyldithiocarbamate). The results from the structural analogue zinc bis(dibuyldithiocarbamate) are taken used (for details see Reporting Format as attached to the respective IUCLID entry and CSR Appendix A.1). A 3-h EC50 value of 1,428 mg/L and a 3-h EC10 value of 166 mg/L is available from a GLP-compliant, OECD 209 guideline study with activated sludge ([redacted]). The 3-h EC50 value is used in the assessment using an assessment factor of 10."*

Documentation of the read-across approach
As explained under section III.B.3 above the Registrant has provided justifications for using an analogue approach for environmental endpoints in Annex A1 of the CSR. The Registrant has followed the reporting format provided in ECHA Guidance R6 QSARs and grouping of chemicals and gave a hypothesis for the analogue approach (please refer to section III.B.3 above. In this Annex A1 the Registrant reports *"Comparing all available experimental results on aquatic toxicity of ZBEC, ZDBC, ZDEC and ZDMC (see Table 1), it is likely that the toxicity of ZDEC is lower than the toxicity of ZDMC but higher than the toxicity of ZBEC and ZDBC. A trend is observed that with increasing molecular weight, and larger substituents at the nitrogen atom of dithiocarbamate moieties (benzyl or different alkyl chain lengths,) the toxicity decreases. For activated sludge respiration inhibition testing data is available for both ZBEC and ZDBC."* The Registrant furthermore states: *"Comparing all available experimental results on aquatic toxicity of ZBEC, ZDBC, ZDEC and ZDMC (see Table 1), it is likely that the toxicity of ZDEC is lower than the toxicity of ZDMC but higher than the toxicity of ZBEC and ZDBC."*

In support of this hypothesis, the Registrant provided an analogue approach justification and a data matrix, and conclusions per endpoint for C&L, PBT/vPvB and dose descriptor.

Scientific assessment of the analogue approach
The scientific assessment of the analogue approach proposed by the Registrant is discussed above in section III.B.6. In addition to the discussion there, ECHA notes that the read-across for the endpoint activated sludge respiration inhibition is based on the assumption that a trend in aquatic toxicity is observed where *"with increasing molecular weight, and larger substituents at the nitrogen atom of dithiocarbamate moieties (benzyl or different alkyl chain lengths,) the toxicity decreases"*. ECHA notes that no trend in aquatic toxicities can be observed in the data presented by the Registrant in Annex A1. This is contradicting the statement of the Registrant that increasing molecular weight reduces toxicity. Moreover, ECHA could not assess the validity of the data of the other substances in the group (more specifically for this endpoint: ZBEC, ZDBC, ZDMC) since no (robust) study summaries were submitted in the dossier. Furthermore, the Registrant himself has stated that it is likely that the toxicity of ZDEC (substance registered) is higher than the toxicity of ZDBC (proposed analogue substance for activated sludge respiration inhibition testing). ECHA therefore considers that as no clear trend in aquatic toxicities is present the Annex XI (1.5) requirement of *"a constant pattern in the changing of the potency of the properties across the category"* is not met and the read-across proposal is not accepted for the endpoint of Annex VIII, Section 9.1.4 activated sludge respiration inhibition testing.

As explained above, the information available 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 acknowledge that the Registrant in this comments agreed to conduct the requested test.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Activated sludge, respiration inhibition test (carbon and ammonium oxidation) (test method OECD 209).

7. Effects on terrestrial organisms

The Registrant must address the standard information requirements set out in Annexes IX and X, section 9.4., for different taxonomic groups: effects on soil micro-organisms (Annex IX, section 9.4.2.), short-term toxicity testing on invertebrates (Annex IX, section 9.4.1.), long-term toxicity testing on invertebrates (Annex X, section 9.4.4.), short-term toxicity testing on plants (Annex IX, section 9.4.3.) and long-term toxicity testing on plants (Annex X, section 9.4.6.).

a) Terrestrial Invertebrates (Annex IX, 9.4.1. and Annex X, 9.4.4.)

Toxicity to terrestrial invertebrates is a standard information requirement under Annex IX, 9.4.1. and Annex X, 9.4.4.) of the REACH Regulation. The registration dossier does not contain data for this endpoint. Instead, the Registrant proposed to adapt this standard information requirement by waiving the study: *"In accordance with column 2 of REACH Annexes IX and X, studies on soil toxicity do not need to be conducted as the chemical safety assessment does not indicate the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. A refinement of*

the PNEC for soil calculated with the equilibrium partitioning method with experimental data is not required."

Based upon the available aquatic toxicity information and the physico-chemical properties of the substance, and in relation to section R.7.11.6., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (May 2008), ECHA considers that the substance would fall into soil hazard category 4. Therefore ECHA does not agree that the assessment of the available data indicates no need to investigate further the effects of the substance. As the Registrant has not justified an adaptation of the standard information requirement there is an information gap, which needs to be filled.

The earthworm reproduction test (OECD 222), Enchytraeid reproduction test (OECD 220), and Collembolan reproduction test (OECD 232) are each considered capable of generating information appropriate for the fulfilment of the information requirements for long-term toxicity testing to terrestrial invertebrates. Each of these tests is suitable to also address the information requirement of Annex IX, section 9.4.1. ECHA is not in a position to determine the most appropriate test protocol, since this decision is dependent upon species sensitivity and substance properties.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is required to submit the following information derived with the registered substance subject to the present decision: Long-term toxicity to terrestrial invertebrates (Annex X, 9.4.4.); test method: Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*) OECD 222, Enchytraeid reproduction test OECD 220 or Collembolan reproduction test (OECD 232).

b) Terrestrial Plants (Annex IX, 9.4.3. and Annex X, 9.4.6.)

Toxicity to terrestrial plants is a standard information requirement under Annex IX, 9.4.3. and Annex X, 9.4.6.) of the REACH Regulation. The registration dossier does not contain data for this endpoint. Instead, the Registrant proposed to adapt this standard information requirement by waiving the study: *"In accordance with column 2 of REACH Annexes IX and X, studies on soil toxicity do not need to be conducted as the chemical safety assessment does not indicate the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. A refinement of the PNEC for soil calculated with the equilibrium partitioning method with experimental data is not required."*

Based upon the available aquatic toxicity information and the physico-chemical properties of the substance, and in relation to section R.7.11.6., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (May 2008), ECHA considers that the substance would fall into soil hazard category 4. Therefore ECHA does not agree that the assessment of the available data indicates no need to investigate further the effects of the substance. As the Registrant has not justified an adaptation of the standard information requirement there is an information gap which needs to be filled.

Both the Terrestrial plants, growth test (OECD 208, in the configuration as explained below) and the Soil Quality – Biological Methods – Chronic toxicity in higher plants (ISO 22030) are considered capable of generating information appropriate for the fulfilment of the information requirement for long-term toxicity testing on plants. Each of these tests is suitable to also address the information requirement of Annex IX, section 9.4.3. ECHA is not in a position to determine the most appropriate test protocol, since this decision is dependent upon species sensitivity and substance properties.

OECD guideline 208 (Terrestrial plants, growth test) considers the need to select the number of test species according to relevant regulatory requirements, and the need for a reasonably broad selection of species to account for interspecies sensitivity distribution. For long-term toxicity testing, ECHA considers six species as the minimum to achieve a reasonably broad selection. The long-term toxicity testing shall be conducted with species from different families, as a minimum with two monocotyledonous species and four dicotyledonous species, selected according to the criteria indicated in the OECD 208 guideline. The Registrant should consider if testing on additional species is required to cover the information requirement.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is required to submit the following information derived with the registered substance subject to the present decision: Long-term toxicity testing on plants (Annex X, 9.4.6.); test method: Terrestrial plants, growth test (OECD 208), with at least six species tested (with as a minimum two monocotyledonous species and four dicotyledonous species) or test method: Soil Quality – Biological Methods – Chronic toxicity in higher plants (ISO 22030).

c) Soil microorganisms (Annex IX, section 9.4.2.)

The hazard to soil microbial communities is a standard information requirement under Annex IX, section 9.4.2. of the REACH Regulation. The registration dossier does not contain data for this endpoint. Instead, the Registrant proposed to adapt this standard information requirement by waiving the study: *"In accordance with column 2 of REACH Annexes IX and X, studies on soil toxicity do not need to be conducted as the chemical safety assessment does not indicate the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. A refinement of the PNEC for soil calculated with the equilibrium partitioning method with experimental data is not required."*

The Registrant has not provided any justification for an adaptation argument, which he – based on his chemical safety assessment – found to be fulfilled. Furthermore, ECHA emphasises that the intrinsic properties of soil microbial communities are not addressed through the EPM extrapolation method and therefore the potential adaptation possibility outlined for the information requirement of Annex IX, Section 9.4.1. does not apply for the present endpoint. Further, ECHA notes that the requested tests under subsections (a), (b) above are not sufficient to address this standard information requirement.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is required to submit the following information derived with the registered substance subject to the present decision: Effects on soil micro-organisms (Annex IX, 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216).

In his comments, the Registrant disagrees with the need for terrestrial testing, based on five main reasons:

1. Column 2: the use of EPM
   "First, according to REACH Annex IX, section 9.4, column 2
   "in the absence of toxicity data for soil organisms, the equilibrium partitioning method (EPM) may be applied to assess the hazard to soil organisms. The choice of the appropriate tests depends on the outcome of the chemical safety assessment". Using the equilibrium partitioning method, the highest PEC/PNEC value calculated is 0.013 which is well below"
   REACH does not impose limitations on the use of EPM and it does not authorize ECHA to exclude the use of EPM for any testing on terrestrial organisms.

The third paragraph of Annex IX, section 9.4, column 2 states that "for substances that have a high potential to adsorb to soil or that are very persistent, the registrant shall consider long-term toxicity testing instead of short-term."
Indeed, ZDEC has a high potential to adsorb to soil, but the CSA indicates that no short-term tests have to be performed. Hence this part of column 2 does not apply to ZDEC."

2. Column 2: "based on the CSA"
   "Secondly, according to REACH Annex X, section 9.4, column 2
   "Long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment according to Annex I indicates the need to investigate further the effects of the substance and/or degradation products on terrestrial organisms. The choice of the appropriate test(s) depends on the outcome of the chemical safety assessment."
   Although the use of the equilibrium partitioning method is not specifically mentioned here, it is also not excluded. Since the chemical safety assessment using the equilibrium partitioning method does not indicate that ZDEC has a risk to the environment, long-term toxicity testing is not necessary."
3. Guidance 7c is inconsistent with the legal text
   "Thirdly, according to ECHA Guidance 7c, the potential hazard of a substance, not the CSA, determines which tests have to be performed. This guidance, however, is inconsistent with REACH, Annex X, section 9.4, column 2, which designates the CSA, not potential hazard, as the proper yardstick for determining whether testing is required and selecting the appropriate testing. REACH states as follows: "Long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment according to Annex I indicates the need to investigate further the effects of the substance and/or degradation products on terrestrial organisms. The choice of the appropriate test(s) depends on the outcome of the chemical safety assessment." (emphasis added) The selection of the appropriate test must further be based on the CSA under Annex IX, section 9.4: "The choice of the appropriate test(s) depends on the outcome of the chemical safety assessment." (emphasis added)
   From REACH Annex IX and X, section 9.4, column 2 it is clear that the both hazard and exposure have to be taken into account. Therefore, ECHA's request to limit the assessment to the potential hazards of a substance is not in line with the REACH Regulation. The Draft Decision would be in breach of REACH by limiting the assessment to hazards without taking into account the risks.
4. *ECHA's authority in compliance checks*
   In the context of compliance checks, ECHA's authority is limited to verifying compliance with the pertinent provisions of REACH cited in Article 41(1). ECHA has no general authority to adapt the REACH requirements; only where REACH so provides, ECHA has the authority to impose its own judgments. Given that REACH does not grant ECHA such authority in this instance, the Draft Decision would be ultra vires because it would require the submission of information based on criteria that are different from (or even more restrictive than) those provided by REACH. Likewise, the issuance of the pertinent Guidance by ECHA may constitute a misuse of power insofar as the Guidance intends to expand the scope of REACH and thus amend it outside a legislative procedure for the adoption of amendments.7
5. Annex IX, 9.1 vs. 9.4 and CSA considerations
   Finally, column 2 of REACH Annex IX 9.1 regarding long-term testing for aquatic toxicity is identical to REACH Annex X, section 9.4, column 2. ECHA considers the use of the chemical safety assessment appropriate only in deciding whether long-term aquatic toxicity tests are required, not with respect to long-term terrestrial toxicity. This suggests that ECHA is not consistent in its interpretation of the REACH Regulation, and ECHA has not provided any justification for this difference in

interpretation. Of course, there is no such justification and ECHA should consider the CSA in both cases.
In the case of ZDEC, the risk characterization for the terrestrial compartment results in PEC/PNEC ratios well below 1. The highest is 0.013 for grassland if ZDEC is used as a vulcanisation agent in rubber and latex production. In R10.6.1, it is stated that the PECsoil/PNECsoil ratio needs to be increased by a factor of 10 for compounds with a log Kow >5 (or for compounds with a corresponding absorption or binding behavior, e.g. ionisable substances).
Even when this factor of 10 is applied, however, the PEC/PNEC ratio will not be higher than 1. The CSA demonstrates that there is no risk that is inadequately controlled and there, therefore, is no indication that further investigation of the effects of the substance and/or degradation products on terrestrial organisms is needed. Accordingly, the registrant is allowed to apply the adaptation provided by REACH, Annex X, section 9.4, column 2."

ECHA disagrees with the Registrant for the reasons outlined below.

1. Column 2: the use of EPM
   REACH Annex IX, section 9.4, column 2, indeed mentions that "*...(EPM) may be applied...*". However, even though not explicitly mentioned in the legal text it is obvious and clear that the use of EPM is limited to cases where EPM is (scientifically) applicable. The ECHA guidance (R.7.11.6., Chapter R.7c of the ECHA Guidance on information requirements and chemical safety assessment, May 2008) explains this further, for instance on p. 105: "*...(EPM) this approach should be limited to screening purposes only.*" And on p. 121: "*The use of the EPM method, however, provides only an uncertain assessment of risk and, while it can be used to modify the standard data-set requirements of Annex IX and X, it cannot alone be used to obviate the need for further information under this Annex.*" Most importantly in this case, as mentioned in the DD sent to the Registrant, ECHA concludes that based on the physico-chemical and ecotoxicological properties the substance falls into soil hazard category 4. The guidance document R.7c states that EPM cannot be applied in such cases: in Table R.7.11-2 it is stated that for such substances "*Screening assessment based on EPM not recommmended, intrinsic properties indicate a high hazard potential to soil organisms*" and "*Conduct long-term toxicity tests according to the standard information requirements of Annex X (invertebrates and plants), choose lowest value for derivation of PNECsoil*". As explained in the DD sent to the Registrant, long-term experimental studies on the 3 trophic levels need to be performed. This is further confirmed by the third paragraph of Annex IX, section 9.4, column 2 quoted by the Registrant in his comment: "*for substances that have a high potential to adsorb to soil or that are very persistent, the registrant shall consider long-term toxicity testing instead of short-term.*"
   The Registrant in his comment states that the registered substance has a high potential to adsorb to soil. Furthermore, ECHA notes that the substance should – with the current (lack of) data in the dossier – be considered as P or vP. ECHA disagrees with the Registrant that "*the CSA indicates that no short-term tests have to be performed*". Hence this part of column 2 does not apply to ZDEC" for the following reasons:
   - As outlined above, the soil hazard category 4 in itself leads to the necessity of long-term testing for all 3 trophic levels.
   - The lack of concern from the CSA is based on a PNECsoil derived with EPM; as explained above, EPM is not applicable to soil hazard category 4 substances and therefore a basic parameter (PNECsoil) underpinning the CSA is flawed.
2. Column 2: "based on the CSA"

ECHA disagrees with the Registrant's reasoning that column 2 allows for EPM because the contrary is not mentioned. As explained above, EPM is not applicable to soil hazard category 4 substances.

3. Guidance 7c is inconsistent with the legal text
   ECHA does not consider the guidance to be contradicting the legal text. The legal text refers to the CSA and not RCRs as a determining factor for deciding on testing. Since from the CSA the properties (physico-chemical, fate and ecotoxicological) lead to the conclusion that there is a high hazard potential for soil and to the conclusion that the screening method EPM is not applicable to the registered substance, the CSA indicates the need to perform (long-term) toxicity testing on terrestrial organisms. Moreover and as explained above, ECHA concludes that for a soil hazard category 4 substance, the RCRsoil cannot be calculated without experimental data and therefore the Registrant cannot use this argument to waive testing. ECHA disagrees that for all cases exposure and hazard need to be taken into account for 2 reasons:
   - The legal text does not state anywhere that 'based on the CSA' is limited to RCR's or that always both exposure and hazard should be taken into account.
   - In this particular case, the Registrant has used a flawed (EPM-based) PNECsoil.
4. ECHA's authority in compliance checks ECHA considers that the Registrant's comment is based on a different mistaken interpretation of the REACH Regulation than that considered by ECHA. The testing proposal examination process for Annex IX and X information requirements is foreseen so that ECHA can ensure that such higher-tier testing is tailored to real information needs (Recital 63 of REACH). Where a Registrant has neither adapted an Annex IX or X information requirement in a justified manner, nor complied with his obligation to make a testing proposal, the testing proposal examination process is not triggered. When ECHA identifies such incompliance, the compliance check process pursuant to Article 41 of the REACH Regulation is the appropriate tool to achieve the compliance of the registration with the applicable information requirements. Requiring the submission of a testing proposal would not achieve compliance with the information requirement (Article 43), 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. Therefore, the (draft) decision is not *ultra vires*.
5. Annex IX, 9.1 vs. 9.4 and CSA considerations
   As for the fact that "*ECHA considers the use of the chemical safety assessment appropriate only in deciding whether long-term aquatic toxicity tests are required, not with respect to long-term terrestrial toxicity*" ECHA notes that a similar approach is taken for long-term aquatic studies. Similar to the impact of substance properties on the use of EPM, if a substance, due to its properties, would fall outside the applicability of the OECD guideline, the Registrant would not be allowed to use this guideline.
   As already explained above, the PNECs and RCRs the Registrant refers to in his comment are flawed and cannot be used to obviate testing needs. ECHA also notes that due to the requests under A.5 above and B.2 below, the PNECaquatic in the current dossier is incorrect. This incorrect PNECaquatic has been used by the Registrant for deriving a PNECsoil using EPM. As explained above, EPM cannot be used in this particular case.

d) Notes for consideration by the Registrant:

For substances that fall into soil hazard category 4 (as the registered substance does) it is not possible to adapt one of the requested long-term studies ((a) and (b) above) with the results obtained from the other long-term study for soil requested by the present decision and an initial screening assessment based upon the Equilibrium Partitioning Method (EPM). The Guidance foresees that long-term toxicity tests according to the standard information requirements of Annex X should be carried out and that the lowest value obtained should be used to derive the PNEC soil.

B. Information related to the chemical safety assessment and chemical safety report

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation the registration shall contain a chemical safety report (CSR) which shall document the chemical safety assessment conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

1. Revised DNELs for workers and for the general population and inclusion of justifications for any deviations

Pursuant to Annex I, 1.0.1 and 1.4.1 of the REACH Regulation, Derived No-Effect Levels (DNELs) shall be established for the substance based on the available information, reflecting the likely route(s), duration and frequency of exposure.

Annex I, 1.4.1 of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:
- the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
- the nature and severity of the effect;
- the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies.

Annex I, 1.4.1 also requires that a full justification for the establishment of DNELs is given specifying, among others, the choice of information used, the route of exposure and the duration and frequency of exposure of the substance.
The ECHA "Guidance on information requirements and chemical safety assessment" (Volume 8, R.8, November 2012) provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information.

ECHA observes that the Registrant has not followed the recommendations of ECHA's Guidance R.8 and has not provided a full justification for the derivation of DNELs (long term dermal and inhalation for workers and the general population) in line with Annex I, 1.4.1. Instead, the Registrant has applied less protective assessment factors than those recommended by the ECHA guidance:
- He did not follow the ECHA Guidance R.8 for extrapolation from oral studies in experimental animals to inhalation in humans;
- He has not applied assessment factors to cover uncertainties due to remaining interspecies differences (i.e. not related to allometric scaling), ECHA guidance 2.5;
- The assessment factor for the intraspecies extrapolation for workers is selected as 3, ECHA guidance recommends 5;

- The assessment factor for the intraspecies extrapolation for the general population is selected as 5, the ECHA Guidance recommends 10;
- The default factor for quality of the database (default 1) is only applicable for a good/standard quality of the database. The chronic toxicity study used to derive the starting point is not condsidered by ECHA as a study which covers the information requirement for repeated dose toxicity; in addition the 2-generation study was not conducted with the registered substance and a prediction was used; a higher assessment factor (than the default of 1) should have been used according to the ECHA Guidance R.8.

No substance-specific justifications have been provided for the deviations from the Guidance. Reference to an ECETOC publication cannot replace substance specific justifications.

ECHA concludes that the derivation of DNELs has not been conducted according to Annex I, 1.4.1. of the REACH Regulation. The Registrant shall reconsider his DNELs and reassess related risks and include the revision and any relevant considerations and justifications in the CSR. In the reassessment, the Registrant shall follow ECHA Guidance, or in the event of deviation, shall fully justify such deviation. Such justification would for example be necessary for

- the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
- the nature and severity of the effect;
- the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
- and that the DNELs reflect the likely route(s), duration and frequency of exposure.

ECHA acknowledge that the Registrant in this comments agreed to re-consider the DNEL derivation.

Once the results of the tests required under Section II.B.43 to 6 are available the DNELs shall be revised further taking the new results into account and following the same principles outlined above.

Note for consideration by the Registrant

Any change in the DNELs will lead to the need to revise the exposure assessment (Annex I, 5) and risk characterisation (Annex I, 6) accordingly.

2. Revised PNECs for Freshwater, Marine water, Sediment (marine water), Sediment (freshwater) and Soil (Annex I, sections 3.0.4. and 3.3.)

According to Annex I, 3.0.1, one of the objectives of the environmental hazard assessment is to identify the concentration of the substance below which adverse effects in the environmental sphere of concern are not expected to occur. This concentration is known as the Predicted No-Effect Concentration (PNEC). Annex I, Section 3.3. of the REACH Regulation requires the registrant to establish PNECs for the registered substance, covering each environmental sphere. The PNECs may be calculated applying an appropriate assessment factor to the effect values (see the ECHA Guidance Document chapter R.10). If it is not possible to derive a PNEC, this shall be clearly stated and justified.

PNEC freshwater

ECHA notes that under section 6 of IUCLID (Endpoint summary: Ecotoxicological information) the Registrant has first indicated that an assessment factor of 100 has been used for the derivation of the PNEC freshwater. However, in the justification field the Registrant writes the following: *"The assessment factors were set from 50 to 10. Data for chronic toxicity to algae is lacking, but this is the least sensitive trophic level. Chronic data is available for fish and invertebrates, thus this covers the lack of chronic data for algae."* ECHA notes that an AF of 10 as written in the justification field has been used in the PNEC derivation.

The footnote to Annex I, Section 3.3.1. provides information on the application of assessment factors to cover the uncertainty associated with the available data, indicating that an assessment factor of 1000 is typically applied to the lowest of three short term L(E)C50 values derived from species representing different trophic levels and a factor of 10 is applied to the lowest of three long-term NOEC values derived from species representing different trophic levels. This is further explained in the ECHA guidance Chapter R.10 (May 2008). ECHA guidance notes further that a factor of 10 can also be applied to the lowest long-term result from only two species if with high probability it can be determined that the most sensitive species has been examined. According to ECHA Guidance Chapter R10 (May 2008) an assessment factor of 50 can be applied to the lowest of two long-term (EC_{10} or NOEC) results covering two trophic levels when such result have been generated covering that level showing the lowest L(E)C50 in the short term tests. An assessment factor of 100 should be used if a single long-term result (fish or *Daphnia*) is available if this result was generated for the trophic level showing the lowest L(E)C50 in short-term tests.

ECHA notes that the Registrant has used an AF of 10. ECHA further notes that the lowest NOEC of 3.2 ug/L obtained from a chronic *Daphnia magna* study has been used as the basis of the PNEC derivation.

However, ECHA disagrees with the chosen assessment factor for the following reasons:

1. As explained in secton III.B.7 above, ECHA concludes that the study reported under IUCLID section 6.1.2 is not compliant as a long-term toxicity study on fish.
2. The Registrant concludes that data for chronic toxicity to algae is not available, but still adapts the assessment factor assuming that enough information is available for algae without chronic algae toxicity data. However, the Registrant's claim of algae being *"the least sensitive trophic level"* is not valid as acute toxicity to algae is only 4 times lower than corresponding acute toxicities of invertebrates and fish, whereas according to ECHA Guidance R7B (version 1.2 November 2012) a difference of 10 times can be used to state that one species is more sensitive than another. Therefore, ECHA considers that it has not been shown that one of the three aquatic species used in testing is most/least sensitive.

ECHA acknowledge that the Registrant in this comments agreed to provide the requested information.

Therefore, ECHA concludes that only for one trophic level (aquatic invertebrates) a compliant long-term study is available and an assessment factor of 100 should have been used, in line with Table R.10-4 of Guidance on information requirements and chemical safety assessment, Chapter R.10: Characterisation of dose [concentration]-response for environment (version May 2008). Therefore, the Registrant should update the PNEC, using a fully justified assessment factor.

PNEC marine water

In the justification field for the PNEC marine water calculation in IUCLID secton 6 the Registrant writes the following: *"The assessment factors were set from 500 to 100. Data for chronic toxicity to algae is lacking, but this is the least sensitive trophic level. Chronic data is available for fish and invertebrates, thus this covers the lack of chronic data for algae."*

However, based on the currently available compliant aquatic toxicity data in the dossier – as further explained in section III.D.2 PNEC freshwater – an assessment factor of 1000 should be applied to the result of the long-term *Daphnia* study, in line with Table R.10-5 of Guidance on information requirements and chemical safety assessment, Chapter R.10: Characterisation of dose [concentration]-response for environment (version May 2008). Therefore, the Registrant should update the PNEC, using a fully justified assessment factor.

PNEC sediment (marine water and freshwater)

In the justification field for the PNEC sediment marine water and freshwater calculation in IUCLID secton 6 the Registrant writes the following: *"The equilibrium partitioning method was used using a calculated Koc value of 14,750 L/kg."* ECHA notes that in using the Equilibrium partitioning method (EPM) the Registrant has used the PNEC freshwater and PNEC marine water in deriving the respective PNEC sediment freshwater and marine water values. As these PNEC calculations have used unjustified AFs as discussed above in section III.D.2 PNEC freshwater, also the resulting EPM calculations are not valid. Therefore, the Registrant is requested to revise the PNEC sediment marine water and PNEC sediment freshwater derivation using the PNEC freshwater and PNEC marine water derived with fully justfied assessment factors as explained above.

PNEC soil

Reference is made to section III.B.10, including the notes for consideration by the Registrant (B.10.d).

Note for consideration by the Registrant

Any change in the PNECs will lead to the need to revise the exposure assessment (Annex I, 5) and risk characterisation (Annex I, 6) accordingly.

3. Revised exposure assessment and risk characterisation for the inhalation route (Annex I, 5, Annex I, 6).

Pursuant to sections 0.6.2 and 0.6.3 of Annex I of the REACH Regulation the chemical safety assessment (CSA) performed by a Registrant shall include an exposure assessment according to section 5 of Annex I, as the substance fulfils the classification criteria for several human health hazard classes. Annex I, section 5.2.4 of the REACH Regulation, requires the Registrant to perform an estimation of the exposure levels for all human populations (workers, consumer and humans liable to exposure via the environment) for which exposure to the substance is known or reasonably foreseeable. Each relevant route of exposure (inhalation, oral, dermal and combined through all relevant routes and sources of exposure) shall be addressed. In addition, Annex I, section 5.2.5 of the REACH Regulation indicates that appropriate models can be used for the estimation of exposure levels.

Pursuant to Annex I 6.5, for those human effects for which it was not possible to determine a DNEL a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out.

Risk management measures designed to prevent potential irritant effects have not been addressed in the exposure assessment within the CSR. Some exposures have been assessed at around 6.0 mg/m^3 but the outcome is compared only with the DNEL derived for systemic effects (12 mg/m^3) and risk management measures proposed to protect against these systemic effects. Although the evidence may not currently exist to derive a DNEL for irritant effects, this aspect needs to be considered within the CSR and to provide evidence that irritant effects via inhalation will be avoided, through application of appropriate risk management measures. These risk management measures may need to be different from those currently determined to address systemic exposure. If quantitative data are considered as necessary the Registrant should submit a testing proposal for repeated dose toxicity using inhalation as exposure route. (see section III.B.3).

Clarification of the levels of exposure for some tasks could be provided through revised modeling or presentation of real exposure data. Alternatively, to address the issue of irritancy in the absence of data, a robust qualitative approach is required to demonstrate safe use.

ECHA acknowledge that the Registrant in this comments agreed to provide the requested information.

Therefore, according to Annex I, Section 5, and Annex I, Section 6, the Registrant is requested to provide a revised exposure assessment and revised risk characterisation that demonstrates safe use.

C. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also contained a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) (Annex X, Section 8.7.3.). As these studies are not addressed in the present decision, ECHA Secretariat considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

In carrying out the studies required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Guilhem de Seze, Head of Unit, Evaluation E1

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