ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 27 September 2017

Addressee: [redacted]
[redacted]
Belgium
Decision number: CCH-D-2114370485-44-01/F
Substance name: DISULFIRAM
EC number: 202-607-8
CAS number: 97-77-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 09/10/2013
Registered tonnage band: Over 1000

DECISION ON A COMPLIANCE CHECK

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

1. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance;**

2. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;**

3. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **3 April 2019**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

Appeal

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

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

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

Appendix 1: Reasons

0. Grouping of substances and read-across approach

ECHA based its decision on the evaluation of your registration dossier that contains for the endpoints *Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)*, *Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.*) and *Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.*) adaptation arguments in form of a grouping and read-across approach under Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your read-across approach (sections 0.1, 0.2, 0.3) in general before assessing the individual endpoints (sections 1, 2, 3).

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 similar substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met". According to Annex XI, section 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for the reference substance(s), and the data should be adequate for the purpose of classification and labelling and/or risk assessment. The REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards. In accordance with these objectives and the objectives of the Compliance Check process, ECHA shall assess whether a prediction of the relevant properties of the substance subject to this decision by using the results of the proposed read-across is acceptable based on the information currently available.

0.1 Description of the grouping and read-across approach proposed by the Registrant

You have sought to adapt the environmental information requirements for *Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)*, *Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.*) and *Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.*) by applying a read-across approach according to Annex XI, Section 1.5.

You propose read-across between the structurally similar substance, thiram (tetramethylthiuram disulphide), EC No 205-286-2 (CAS No 137-26-8) as source substance and the substance subject to this decision, disulfiram, EC No 202-607-8 (CAS No 97-77-8) as target substance. ECHA notes that you have also provided data from a second analogue substance, ziram (zinc (bis) dimethyldithoiocarbamate), EC No 205-288-3 (CAS No 137-30-4). However, as these endpoints for which you used this substance as a source substance are not part of this decision, ECHA did not assess the read-across approach for this source substance.

Your dossier contains read-across documentation as a separate attachment in Section 13 of the technical dossier in IUCLID ([redacted]). In addition, in the read-across justification document you indicate that "*Thiram and Disulfiram were evaluated as members of the so-called Thiuram Category in the frames of the High Production Volume Challenge Program (US EPA, September, 2009)*".

You further refer to a "[redacted] *(in attachment)*", but ECHA notes that this document is not attached to the technical dossier. ECHA understands that you justify your read-approach also based on the evaluation by US EPA agreeing that the read across could be used between thiram and disulfiram. However, since this document is not available in your technical dossier, ECHA cannot verify whether this could be used as a valid justification.

You use the following arguments to support the prediction of properties of the registered substance from data of the source substance:

- On the basis of structural similarity and similarity in physico-chemical, environmental fate and pathways and environmental toxicity, it is possible to predict the ecotoxicological properties of the registered substance (section 4 of your document "[redacted]").
- The source substance and the registered substance are both mono-constituent substances with a purity above 90% and impurities are not expected to have any impact on the physico-chemical profile and toxicity (section 3 of your document "[redacted]").

According to you the source and registered substances have similar properties for the above-mentioned information requirements.

ECHA considers that this information is your read-across hypothesis, which provides the basis whereby you predict the properties of the registered substance from the source substance.

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

Based on the information provided in your registration dossier, ECHA concludes that the properties of the source and the registered substance differ, as outlined below.

Structural similarity

According to the provisions of Annex XI, section 1.5 of the REACH Regulation, structural similarity is a prerequisite for applying grouping and read-across approaches. However, structurally similar substances still exhibit differences in their chemical structures. The impact of these structural differences on the properties of the substances needs to be accounted for in the read-across hypothesis in order to establish that the properties of the target substance can be predicted from data on the source substance.

You state the following : "*The target chemical is Disulfiram (tetraethyl thiuram disulfide, TETD, CAS-No. 97-77-8). Its molecular structure contains two ethyl groups attached to a nitrogen atom, which is attached to a molecule of carbon disulfide. Two such identical units are linked through a disulfide bridge. A known analogue for TETD is Thiram (TMTD, CAS-No. 137-26-8), where ethyl groups are replaced by methyl groups.*" (section 1 of your document "[redacted]").

ECHA observes that the source and target substances in this read-across approach exhibit structural differences. Specifically, both source and target substance indeed share a similar - relatively small - core structure, but the target substance has 4 ethyl group side chains, while the source substance has 4 methyl side chains. These differences may have a potential to influence the physico-chemical and ecotoxicological properties of the substances, as discussed below. You have not provided in your read-across hypothesis an assessment supported by scientific justifications of the impact of these structural differences between the source and the target substances on the properties of these substances.

Support of a similar or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances*". One prerequisite for a prediction based on read-across therefore is that the substances involved are structural similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

You state that "*Altogether the physico-chemical properties of the three substances can be considered similar.*" ECHA acknowledges that you have provided a data matrix in Table 3 of the read-across document to allow comparison of physicochemical properties between the target and the source substances. ECHA notes that the target and source substances have different water solubities (4.09 mg/L at 25°C for disulfiram and 17.1 mg/L at 20°C and pH 7 for thiram) and partition coefficients (Log Kow of 3.6 for disulfiram and 1.73 for thiram). Thus, based on the data provided, it cannot be concluded that the substances have similar physico-chemical properties.

Therefore, ECHA disagrees with your statement that the physicochemical properties of the target substance are similar to those of the source substance.

The differences are considerable and likely lead to differences in environmental fate and ecotoxicological properties. The differences in water solubility and partition coefficient for instance can have an impact on the bioavailability of the substances during the ecotoxicity tests, as well as on the prediction of ecotoxicity properties. Regarding the prediction of ecotoxicity, you have indicated that "*due to the reactive toxicity of dithiocarbamates, log Kow is not considered to be the predominant trigger of ecotoxicity.*" However, since the target substance has a higher Log Kow than the source, it has a higher potential to be taken up and to accumulate, and this might cause stronger effects. However, you did not submit any further information to show that the likely higher internal concentrations of the target substance (due to the higher logKow, lower water solubility) will not influence the prediction.

ECHA notes that the results of the acute toxicity to fish is comparable for the two substances (0.067 mg/L for disulfiram and 0.046mg/L for thiram, i.e. 2.3E-7 mol/L and 1.9E-7 mol/L, respectively, when converted to molar concentrations), but the target substance is more toxic to *Daphnia* in short-term tests (0.15 mg/L for disulfiram and 0.38mg/L for thiram, i.e. 0.5E-6 mol/L and 1.6E-6 mol/L, respectively, when converted to molar concentrations).

Since these two acute bridging studies (*Daphnia* and fish) show that disulfiram is more toxic than thiram in aquatic invertebrates, and since disulfiram is expected to be present at higher internal concentrations in long term tests due to higher Log Kow, the source substance might not provide the worst case estimation of the toxic potential of the registered substance for the prediction of long-term toxicity in fish and aquatic invertebrates. Furthermore, a long-term fish study on the registered substance has also been attached to the technical dossier, where a 10d-NOEC of 3.2 µg/L (1.1E-8 mol/L) is reported (key, OECD TG 210, non GLP, Report no. [redacted], 1991). As explained below under section 3, this result is not meeting the information requirement of long-term toxicity on fish, but it still gives an indication that the registered substance might be more toxic in long-term fish tests than the source substance, for which a 33d-NOEC of 4.6 µg/L (1.9E-8 mol/L) is reported for the source substance (key, OECD TG 210, GLP, Report no. [redacted], 2008).

In conclusion, the source substance might not provide the worst case estimation of the toxic potential of the registered substance. ECHA concludes that you have not adequately explained how the differences in chemical structure, physico-chemical properties and bioaccumulation potential between the target and source substances affect the prediction of ecotoxicity. Moreover, the data seem to suggest that the target substance might be more toxic than the source substance.

In view of these differences, the information provided in the dossier contradicts your read-across hypothesis that the properties of the source and registered substances are similar. Accordingly, your read-across hypothesis is not a reliable basis whereby the properties of the registered substance may be predicted from data of the source substance.

0.3 Conclusion on the grouping and read-across approach

ECHA concludes that you have not provided in your read-across hypothesis an assessment - supported by scientific justifications - on how the differences in structure, physico-chemical and ecotoxicological properties between the source and the target substances impact the predictions. Therefore, your read-across hypothesis is not substantiated, and consequently you have not provided a reliable basis whereby the properties of the registered substance may be predicted from data of the source substance.

For the reasons as set out above, and taking into account all of your arguments, ECHA considers that this grouping and read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. of the REACH Regulation. Therefore, this adaptation cannot be accepted and there is a data gap for the endpoints covered by this read-across approach.

In your comments to the draft decision you attached both the '[redacted]) and the '[redacted](US EPA 2009). ECHA has assessed these documents and considers that these documents do not bring any new information or any additional supporting information that fully address the requests in the current draft decision and that in some cases the submitted information actually contradicts your read-across hypothesis. ECHA has outlined this below:

Although the US EPA indicates that disulfiram, thiram and tetramethylthiuram monosulfide could form a so-called thiuram category under the EPA HPV challenge Program, no new information is present in the documents that would clarify the concerns in the draft decision such as bridging studies for the source and target substance that would show similar properties, or an improved justification why differences in physico-chemical properties would not lead to differences in other properties.

In particular, although it is stated in the the US EPA thiuram category document that the properties are 'similar', marked differences between target and source substance are described, for instance logKow = 1.73 for the source, logKow = 3.88 for the target; water solubility for the source is 16.5-30 mg/L and for the target 4.1 mg/L; fish 96h LC50 values range from 0.13 to 0.27 mg/L for the source and from 0.067 mg/L to 0.32 mg/L for the target. ECHA-S notes that the third substance in the US EPA thiuram category (tetramethylthiuram monosulfide) is not used in the read-across for the registered substance for the endpoints subject to the draft decision. ECHA-S also notes that the requirements for forming a category under the EPA HPV Challenge Program can be different than the requirements under REACH Annex XI, 1.5.

Concerning structural similarity, ECHA-S does not dispute the structural similarities of both substances. However, as already explained in section 0.2 of the draft decision, ECHA points out that the likely impact on the substance's properties of the structural difference (4 ethyl side chains in the target substance instead of methyl side chains in the source) has not been sufficiently described or explained in the dossier nor in your comments to the draft decision. ECHA notes that in your comments on the draft decision you recognise that the similarity assessment has not been addressed with sufficient clarity and that you propose to update the dossier with a more detailed scientific justification.

Regarding the 'support of a similar or regular pattern as a result of structural similarity' ECHA notes that in your comments on the draft decision you acknowledge the impact of the structural differences on the physico-chemical properties, which is in contrast to what is reported in the analogue approach justification document in the dossier ("Altogether the physico-chemical properties of the three substances can be considered similar"). ECHA also understands that in your comments on the draft decision you consider the read-across prediction is possible since similar toxicity (to aquatic organisms) is expected based on similar behaviour in the aquatic environment:

- Firstly, you indicate that both source and target undergo rapid abiotic degradation and in water they both hydrolyse rapidly into a common final degradation product (carbon disulfide).
- Secondly, you indicate that the water solubility values are not the same but comparable.

Hence, based on the hypothesis of similar (rapid abiotic) degradation in water leading to common hydrolyis product(s), you conclude that the Log Kow of the parent source and target substances does not to influence long-term aquatic toxicity.

ECHA has assessed these arguments and considers that, while it may be correct that *not only* logKow determines long-term aquatic toxicity, the impact of this parameter should still be considered in the read-across for the following reasons. You quote a hydrolysis half-life of 3.5 days at pH 7 for the source substance thiram in your comments on the draft decision. A half-life of 68.5 days at pH 5, 3.5 days at pH 7 and 6.9 h at pH 9 are reported for the target substance in the dossier, based on read-across from thiram. Therefore, based on this information ECHA considers that significant concentrations of the parent compound will be present during the test(s) and under environmentally relevant conditions. Moreover, the recovery rates of the parent compound in chronic aquatic studies with the source substance was between [redacted]% showing that hydrolysis was not rapid under the test conditions. This is in contradiction to your hypothesis.

Furthermore, you indicate in your dossier that reactive toxicity of dithiocarbamates drives toxicity and this is not influenced by the logKow. In your comments on the draft decision, you repeat that due to "rapid abiotic degradation" and the (rapid) formation of a common breakdown product (CS2) the logKow of the parent compound is not relevant and does not influence toxicity. However, no arguments or evidence are added to justify this statement. In your comments on the draft decision, you acknowledge that the analysis of the data matrix and scientific discussion of the read-across justification can be improved and you propose to do this in an update. In this respect, ECHA notes that dithiocarbamates are known to have different modes of action, caused by the parent compound or different transformation products. Both from your comments on the draft decision and registration dossier, it is not clear whether the parent compound, one or more hydrolysis products, one or more products of metabolism or a combination of any of these would be the main cause of toxicity. Finally, some of the transformation products of source and target will also be different due to the methyl groups and ethyl groups. These will have a different logKow and different uptake/accumulation potential. It is not known from the comments on the draft decision or from the dossier whether such products would be a significant cause of toxicity and whether they would be formed at a similar rate/extent. In conclusion, without more evidence on which compound(s) cause the observed toxicity, ECHA considers it is difficult for you to to provide an acceptable justification for disregarding the effect of logKow on toxicity.

ECHA notes that as described in the draft decision, the current ecotoxicity data in the technical dossier and considering your comments on the draft decision, still support the hypothesis that the target substance is more toxic than the source substance.

In summary, based on the submitted information in the technical dossier and considering your comments on the draft decision, ECHA considers you have not demonstrated that the substances would have similar properties or they would follow a regular pattern in their properties regarding the specific endpoint requests in the draft decision. As a consequence, there is not an adequate basis for predicting the properties of the target substance from the data obtained with the source substances and the read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. of the REACH Regulation. Therefore, ECHA concludes that you have not demonstrated the aquatic toxicities of the target and source substances are similar.

Bearing the above in mind and your indication to update, ECHA notes that the information raised in your comments on the draft decision should be included in the technical dossier and reflected in the read-across justification. While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage.

1. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. 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.

Column 2 of Annex VII, Section 9.1.2 specifies that the study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing 1 key study record for a study on toxicity to aquatic algae and cyanobacteria (key, OECD TG 201/EPA OPP 122-2/EU method C.3, GLP, Report no. [redacted], 1993) with the analogue substance thiram (tetramethylthiuram disulphide) (EC No 205-286-2). You have also provided two supporting studies with "*additional stastistical analysis to calculate EC50 values based on nominal concentrations.*" These studies use the same data as the key study, but EC50 values are recalculated. However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement cannot be accepted.

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

In your comments, you refer to a study with the source substance thiram by Van Leeuwen (1986) that confirms the data currently in the technical dossier. As explained in Section 0 above, ECHA considers based on all submited information within the technical dossier and your comments on the draft decision, the read-across adaptation cannot currently be accepted. ECHA notes that if the data from Van Leeuwen are deemed relevant and reliable, it should be included as part of the technical dossier. As the data are not part of the current technical dossier and no data are provided in your comments on the draft decision, ECHA cannot assess whether these data are sufficient to fulfil the information gap for this endpoint. However, as mentioned above, you can fulfil the information requirement with a valid and documented adaptation. ECHA emphasises that any testing strategy or adaptation is the Registrant's responsibility (see also the paragraph in the decision section explaining adaptation issues).

ECHA notes that the information raised in your comments on the draft decision should be included in the technical dossier and reflected in the read-across justification. While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Algae growth inhibition test, EU C.3./OECD TG 201).

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing 1 study record for a study on long-term toxicity to aquatic invertebrates (key, OECD TG 211, GLP, Report no. [redacted], 2008) with the analogue substance thiram (tetramethylthiuram disulphide) (EC No 205-286-2). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement cannot be accepted.

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

ECHA notes that - although you indicate in your comments on the draft decision that you think the endpoint could be fulfilled using the read-across data - you also agree in your comments on the draft decision to perform the study.

After the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a study on long-term aquatic toxicity to fish (key, OECD TG 210, GLP, Report no. 657A-102, 2008) with the analogue substance thiram (tetramethylthiuram disulphide) (EC No 205-286-2). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement cannot be accepted.

Furthermore, in the technical dossier you have also provided a study record for a study on long-term aquatic toxicity to fish with the registered substance (key, OECD TG 210, non GLP, Report no. [redacted], 1991). You have reported in IUCLID section 6.1.2 about this study: "*Non-GLP-Guideline study, minor restrictions in design and/or reporting but otherwise adequate for assessment*". You also indicate that this study is "*equivalent or similar to OECD Guideline 210 (Fish, Early Life Stage Toxicity Test)*". However, this study does not provide the information required by Annex IX, Section 9.1.6.1 / 9.1.6.2 / 9.1.6.3., because of the following several shortcomings:

- The test duration was only 10 days and you report: "*only eggs were exposed to the test medium*". According to paragraph 3 of OECD TG 210, the fertilised eggs should be exposed to the test concentrations until the fish reach the juvenile life-stage, i.e. for 30 days post-hatch for the species tested zebrafish, as indicated in Annex II of OECD TG 210. The test duration of 10 days is shorter than the exposure duration of 30 days post-hatch for the fish species tested and thus it does not cover all early-life stages.

- You report that "*Daily observations were made on survival of eggs and larvae, hatching and malformations. (..)The NOEC concentrations for survival, hatching and malformations were determined graphically*", but there is no information on abnormal behaviour and on length and weight of the fish at the end of the experiment. These are endpoints that need also to be measured according to paragraphs 26-31 of OECD TG 210.
- There was no analytical monitoring in this study and therefore one of the validity criteria outlined in paragraph 7 of the (current version of the) OECD TG 210 is not fulfilled: "*the analytical measure of the test concentrations is compulsory*". Especially since this is a non-GLP, non-guideline, semi-static study and since the substance is difficult to test (potential hydrolysis, relatively high logKow), exposure to the test substance may be overestimated in the absence of analytical monitoring.
- Five to seven eggs were tested per concentration, but no replicates have been used based on the information in the robust study summary. The OECD TG 210 (paragraph 19) recommends at least 80 eggs to be used, equally divided over at least 4 replicates.
- The light/dark cycle is unclear ("*...under artificial light during working hours*"). The recommended photoperiod is 12-16 hours for the species tested zebrafish, as indicated in Annex II of OECD TG 210.
- The results and discussion section in the IUCLID file is empty. You have not provided any information on the results and interpretation of the study (e.g. tables for the different endpoints, observations, information on statistics used, validity criteria, applicant's summary and conclusion). On that basis, ECHA cannot asses the study fully.

ECHA concludes that the study has several shortcomings and the study design is not sufficient to cover the endpoint of REACH Annex 9.1.6. Moreover, the robust study summary is not sufficiently detailed.

In your comments on the draft decision you agree that the study with the registered substance currently used as a key study "*can be used as supporting information only*" due to the significant deviations from the test guideline. You also agree that the reporting of the study with the source substance thiram is not detailed enough and you indicate that you intend to update the information. You explain that you intend to use the study with the source substance thiram to cover the endpoint, based on an updated read-across justification. ECHA notes that the study with the source substance thiram is well reported and seems well conducted. However, as explained above, ECHA concludes that the read-across adaptation cannot be accepted in its current form and therefore your proposal to use the FELS study on thiram to fulfil the endpoint cannot currently be accepted. However, as mentioned above, you can fulfil the information requirements with a valid and documented adaptation. ECHA emphasises that any testing strategy or adaptation is the Registrant's responsibility (see also the paragraph in the decision section explaining adaptation issues).

After the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage.

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

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Figure R.7.8-4).*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

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

Notes for your consideration concerning requests 1-3

Before conducting the requested test you shall consult the ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b, Section R.7.8.5 to determine the necessity to conduct long-term toxicity testing on aquatic invertebrates.

Currently the long-term toxicity testing is needed in the absence of reliable short-term toxicity data (Request 1 in this decision) and exposure assessment and risk characterisation. However, you may consider adapting long-term toxicity testing when reliable data on short-term toxicity become available, you perform the exposure assessment and update the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

If after the update of the CSA you come to the conclusion, following the ECHA Guidance as mentioned above, that the long-term toxicity tests are still required to refine the risk assessment, you may further consider Integrated Testing Strategy (ITS) for aquatic toxicity. According to the ITS, as described in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially less sensitive than other trophic levels (i.e. fish, invertebrates, algae), long-term studies may be required on both fish and invertebrates. In such case, according to the ITS, the Daphnia study is to be conducted first. If based on the results of the long-term Daphnia study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

If you come to the conclusion that no further investigation of effects on aquatic organisms is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.5 and 9.1.6. taking into account the new data generated by the short-term toxicity studies requested by the present decision and exposure assessment and risk characterisation.

Due to the potential hydrolysis (and relatively high logKow) of the substance, especially at higher pH values, you should consult the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 20 February 2017.

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

ECHA took into account your comments and did not amend the requests.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the tests 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 or imported. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.