EUROPEAN CHEMICALS AGENCY

Helsinki, 19 May 2020

Addressees
Registrants of TMTM_Joint_Submission listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
26 March 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Tetramethylthiuram monosulphide
EC number: 202-605-7
CAS number: 97-74-5

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***24 February 2022***.

A. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. Transgenic rodent somatic and germ cell gene mutation assays (Annex VIII, Section 8.4., column 2; test method: EU B.58/OECD TG 488) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach with the Substance; duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.

   OR

   In vivo mammalian alkaline comet assay (Annex VIII, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum with the Substance.

2. and 3. Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) (Annex VIII, Sections 8.6.1 and 8.7.1.; test method OECD 422) in rats, oral route with the Substance;

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier. You have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa. Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses issues relevant for several requests while

the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

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.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[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 on general considerations

1. Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying (a) read-across approach in accordance with Annex XI, Section 1.5:

1. Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

ECHA has considered the scientific and regulatory validity of your read-across approach in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)'.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

1. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 13.

You read-across between the structurally similar substances: tetramethylthiuram disulphide (EC: 205-286-2 / CAS: 137-26-8) as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: *"substances with a very similar structure would show similar mechanism of toxicity".*

We understand that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects as a result of structural similarity. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

We have assessed the provided information and have identified the following deficiencies with regards to prediction of toxicological properties.

1. Read-across hypothesis

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[2] ECHA Guidance R.6
[3] ECHA Read-across assessment framework (RAAF, March 2017)
[4] ECHA Read-across assessment framework (RAAF, March 2017)- considerations on multi-constituent substances and UVCBs.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance. It should explain why the differences in the chemical structures should not influence the toxicological/ecotoxicological properties or should do so in a regular pattern.

According to the information provided in your dossier you consider that the properties of the Substance can be predicted from information on the source substance as a result of similarities in their chemical structure and physico-chemical properties.

While structural and physico-chemical similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar human health properties. Furthermore, we note that your Substance is a monosulfide, while the source substance is a disulfide. You have not provided a well-formulated read-across hypothesis, which would explain the structural similarities and differences between the source substance and the Substance, and which would further establish why the differences in the chemical structures should not influence the toxicological properties.

2. *Relevance of the supporting information*

According to the ECHA Guidance[5] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In order to support your claim that your Substance and source substance(s) have similar properties for the endpoints under consideration in the read-across approach, you refer to similarities in their acute toxicity, skin irritation, eye irritation, skin sensitisation properties.

Whilst this data set suggests that the substances may have similar properties for acute toxicity, skin and eye irritation, and skin sensitisation, these studies do not inform on the systemic toxicity after repeated dose administration and developmental and reproductive toxicity properties of the Substance and the source substance. Accordingly, this information is not considered as relevant to support prediction of the properties under consideration.

In your comments to the draft decision, you agreed to remove the read-across adaptation for the toxicological part of the dossier.

Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not

[5] ECHA Guidance R.6: Section R.6.2.2.1.f

comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

Appendix A: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. **Transgenic rodent somatic and germ cell gene mutation assays (Annex VIII, Section 8.4., column 2)**
   OR
   ***In vivo* mammalian alkaline comet assay (Annex VIII, Section 8.4., column 2)**

Under Annex VIII to REACH, the performance of an appropriate *in vivo* somatic cell genotoxicity study must be considered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII.

Your dossier contains positive results for the *in vitro* gene mutation study in bacteria which raise the concerns for gene mutation.

Also, your dossier contains the following *in vivo* studies:

(i) Bone marrow chromosomal aberration (according to OECD TG 475, GLP compliant, 1998) with negative results.
(ii) Sex-linked recessive lethal test in *Drosophila melanogaster* (no guideline, no GLP, publication 1983). You disregarded the study as "not reliable".
(iii) Sex-linked recessive lethal test in *Drosophila melanogaster* (no guideline, no GLP, KL 3, publication 1982). You disregarded the study as "not reliable".
(iv) In vivo micronucleus assay (no guideline, no GLP, publication 1983). You disregarded the study as "not reliable".

We have assessed the provided information and identified the following issues:

A. The identified concern not addressed

According to ECHA Guidance R.7a, the *in vivo* somatic cell genotoxicity study must address the specific concern raised by the *in vitro* positive result.

Study (i) is not addressing the gene mutation concern raised by the *in vitro* data, and does not fulfil the information requirement.

B. Studies without adequate and reliable coverage of the key parameters of OECD TG 474

To be considered adequate for this endpoint, the study has to meet the requirements of OECD TG 474, and the key parameters of this test guideline include, among others:

a) A positive control group (or scoring control) that produces a statistically significant increase in the induced response compared with the concurrent negative control.
b) At least 4000 immature erythrocytes per animal must be scored for the incidence of micronucleated immature erythrocytes.

c) The proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes must be reported for each group

of animals.

For study (iv) which reported genotoxicity the above mentioned key parameter(s) are not met because the reported data for the study does not include:

a) A positive control
b) At least 4000 scored immature erythrocytes per animal but only 2000
c) Information on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals.

In the absence of detailed information on this critical aspect of the study, we cannot evaluate the reliability of the conclusions derived from this data.

Furthermore, ECHA notes that you have disregarded studies (ii)-(iv) as "not reliable" (Klimish score 3). We agree that the documentation provided does not allow to assess the reliability of the studies.
Finally, studies (ii) and (iii) are performed on a non-mammalian test system (flies), hence they are not an adequate *in vivo* mammalian study.

Therefore, the provided *in vivo* tests (ii-iv) are not adequate and reliable.

In your comments to the draft decision you agreed to perform an *In vivo* mammalian alkaline comet assay (OECD TG 489), as requested in the draft decision.

ECHA considers that an appropriate *in vivo* follow up mutagenicity study is necessary to address the concern identified *in vitro*.

According to the ECHA Guidance R.7a[6], the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a *positive in vitro* result on gene mutation.

Test design

In case you decide to perform the comet assay, according to the test method OECD TG 489, the test must be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

In case you decide to perform the TGR assay, according to the test method EU B.58/OECD TG 488, the test must be performed in transgenic mice or rats and the test substance is usually administered orally.

[6] ECHA Guidance R.7a, Section R.7.7.6.3

According to the test method EU B.58/OECD TG 488, the test must be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, glandular stomach and duodenum as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum must be stored (at or below −70 °C) until the analysis of liver and glandular stomach is completed; the duodenum must then be analysed only if the results obtained for the glandular stomach and for the liver are negative or inconclusive.

Germ cells

Comet assay
You may consider to collect the male gonadal cells collected from the seminiferous tubules (as described by e.g. O'Brien et al. [7]) in addition to the other aforementioned tissues, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

TGR
You may consider to collect the male germ cells at the same time as the other tissues, in order to limit additional animal testing. According to the OECD 488 the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years (at or below −70 °C). Following the generation and analysis of data on somatic cells, you should consider analysing the collected germ cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

2. Short-term repeated dose toxicity study (28 day), oral route (Annex VIII, Section 8.6.1.)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected. Therefore, the information requirement is not fulfilled.

When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/ developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that

[7] O'Brien, J.M., Beal, M.A., Gingerich, J.D., Soper, L., Douglas, G.R., Yauk, C.L., Marchetti, F. (2014) Transgenic Rodent Assay for Quantifying Male Germ Cell Mutant Frequency. J. Vis. Exp. (90), e51576, doi:10.3791/51576

unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[8]

Information on the design of the study to be performed (species and route)

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and in the Chemical safety Report, ECHA considers that the oral route is the most appropriate route of administration to investigate repeated dose toxicity, as the Substance is a liquid of very low vapour pressure (0.002 Pa at 25°C) and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. Hence, the test shall be performed by the oral route.

According to test method OECD TG 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers that testing should be performed with rats.

3. Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:

- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

The source study you have used in your read-across approach *"Developmental toxicity of ferric dimethyldithiocarbamate and Bis(dimethylthiocarbamoyl) disulside in rats and mice"* is not performed according to a test guideline or GLP requirements. The study design is divided into two parts: the first involved treated male rats mated with untreated females and the second – treated females mated with untreated males.

The study is not performed according to an adequate test method in the meaning of Article 13(3). The second part of the study, investigating the fertility in female rats was conducted

[8] ECHA Guidance R.7a, Section R.7.6.2.3.2.

with two dose levels instead of three, and the exposure duration does not cover the relevant life stages. Concomitant dosing of males and females has not been performed. Thus, the examination of key parameters for sexual function and fertility such as duration of gestation and parturition, have not been monitored as required in EU B.63/OECD TG 421 or EU B.64/OECD TG 422. In addition, key parameters for sexual function and fertility, such as parturition, lactation and weight and histopathology of reproductive organs and tissues have not been measured.

In your comments to the draft decision you agreed to perform a Combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), as requested in the draft decision.

Based on the above, the information you provided do not fulfil the information requirement.

For the reasons explained above under request 2., the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided.

Information on study design

Similarly as explained above under request 2., a study according to the test method EU B.64/OECD TG 422 must be performed in rats with oral administration of the Substance.

Appendix B: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 18 July 2019.

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

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix C: Observations and technical guidance

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

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 the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[9].

4. Test material

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[10].

[9] https://echa.europa.eu/practical-guides
[10] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[11]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[12]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[13]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[11] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[12] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[13] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.