EUROPEAN CHEMICALS AGENCY

Helsinki, 05 August 2020

Addressee
Registrant of JS_PETMA as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
01/08/2019

Registered substance subject to this decision ("the Substance")
Substance name: 2,2-bis[[(mercaptoacetyl)oxy]methyl]-1,3-propanediyl bis(mercaptoacetate)
EC number: 233-482-8
CAS number: 10193-99-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***12 February 2021***.

Requested information must be generated using the Substance unless otherwise specified.

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. / OECD TG 471)

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

Reasons for the request(s) are explained in the Appendix entitled "Reasons to request information required under Annex VII of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH, the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix

entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

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 A: Reasons to request information required under Annex VII of REACH

1. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Annex XI, Section 1.2.

You have provided the following sources of information:

Read-across adaptation (Annex XI, Section 1.5):

a) An in vitro gene mutation study in bacteria (2002) according to OECD TG 471 and GLP, a key study, with an analogue substance Pentaerythritol tetrakis(3-mercaptopropionate, PETMP (EC No. 231-472-8) with the following strains, TA 98, TA 100, TA 1535, TA 1537 and TA 102 which all gave negative results.
b) 2 sets of read across predictions derived from OECD QSAR Toolbox 4.2, Weight of evidence. Based on the prediction the Substance is negative in bacterial reverse mutation assay with and without metabolic activation.

QSAR adaptation (Annex XI, Section 1.3):

c) QSAR prediction using Vega Application (version 1.1.4) with CAESAR Mutagenicity model (version 2.1.13), a supporting study, predicted the Substance as negative for Salmonella in vitro mutagenicity.
d) QSAR prediction using Leadscope Model Applier (version 2.1.2) with Leadscope QSAR Genetic Toxicity – Salmonella model (v3), a key study, predicted the Substance as negative for Salmonella in vitro mutagenicity.

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

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

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

You have not included a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

To fulfil the information requirement, normally a study performed according to OECD TG 471 must be provided. OECD TG 471 requires the study to investigate gene mutations in bacteria as a key parameter using 5 different bacterial strains.

The sources of information (a) to (d) provide relevant information on gene mutations in bacteria.

However, the reliability of the sources of information (a) to (d) is significantly affected by the following deficiences:

A. Validity of read across adaptation relating to the sources of information (a) and (b)

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].

You have provided read-across supporting information in IUCLID Section 7.6.1. entitled: "[redacted]" and "[redacted]" for source information (a).

In the source information (a), you read-across between the structurally similar substances, Pentaerythritol tetrakis(3-mercaptopropionate), EC No. 231-472-8 (CAS No. 7575-23-7) as source substance and the Substance as target substance.

In addition, for source information (b), you have provided two endpoint study records which both include "[redacted]", "[redacted]" and "[redacted]". You provide information on the following analogue substances to support your read-across:

- Acetic acid, mercapto-, neopentanetetrayl ester, CAS No. 10193-99-4
- Pentaerythritol tetrakis (3-mercaptopropionalte) or PETMP, EC No. 231-472-8 (CAS No. 7575-23-7)
- 3-[(3-sulfanylbutanoyl)oxy]-2,2-bis{[(3-sulfanylbutanoyl)oxy]methyl}propyl 3-sulfanylbutanoate or PEMB, EC No. 700-255-4 (CAS No. 31775-89-0)
- 2-ethylhexylthioglycolate or 2-EHTG, EC No. 231-626-4 (CAS No. 7659-86-1)

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

- 2-Chloroethyl-S-carbamoylcysteine, CAS No. 53330-03-3
- Ethyl L-cysteinate, CAS No. 3411-57-3
- Glycoldi(thioglycolate), CAS No. 123-81-9
- Ammonium thioglycolate or ATG, EC No. 226-540-9 (CAS No. 5421-46-5)
- Sodium mercaptoacetate or NaTG, EC No. 206-696-4 (CAS No. 367-51-1)

ECHA notes the following shortcoming with regards to prediction of toxicological properties.

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 substances[5]. 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.

In your read-across supporting information, i.e. "[redacted]" and "[redacted]" for source information (a) and "[redacted]", "[redacted]" and "[redacted]" for source information (b), you have not provided any read-across hypothesis. However, ECHA understands that your read-across hypothesis is that the structural similarity between the source substance(s) and your Substance is a sufficient basis for predicting the properties of your Substance.

While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar human health properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source substance(s) and your Substance.

In your comments to the draft decision, you indicated a general need to improve your category/read-across approach. You provided also a document "[redacted]". This justification document is updated to cover also genotoxicity endpoint.

ECHA understands that it aims to support the source study provided in source information (a) above, in which you read-across between the structurally similar substances, Pentaerythritol tetrakis(3-mercaptopropionate), EC No. 231-472-8 (CAS No. 7575-23-7) as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction:

"The the target and source substances have similar toxicological, ecotoxicological and environmental fate properties because:

- *all substances are small organic molecules;*
- *they share structural similarities with common functional groups: one or more thiol and/or thioether group(s) and carboxylic acid (as free acid, salt or ester);*
- *the metabolism (i.e. ester hydrolysis) leads to comparable products (sulfurcontaining core structure in its acid form and alcohols of differing chains lengths)*
- *in addition, a common mode of action is predicted based on litetrature data, which will be further investigated in vitro*

[5] *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSARs and grouping of chemicals.

The substances were assigned to subgroups according to their main structural features:

- *TGA family: Thioglycolic acid, its salts and esters*
- *3-MPA family: 3-Mercaptopropionic acid, and its esters*
- *TLA family: Thiolactic acid and its salts*
- *Intramolecular-S family: Thiodiglycolic acid or Dithiodiglycolic acid (ammonium salt and Di-2-ethylhexyl-ester), Thiodipropionic acid or Dithiodipropionic acid and its esters, Methylene bis(butyl thioglycolate)*
- *Mercaptans: Thioglycerol, DMDS, DMPT and HIDT*

The acids and salts will dissociate to the respective Thioglycolate or 3-Mercaptopropionate or Thiolactate and the corresponding cation. In case of the esters, the metabolism expected to occur is ester hydrolysis resulting in the corresponding acid and alcohol.[...]

[...] This read-across hypothesis corresponds to scenario 4 of the Read-Across Assessment Framework (RAAF), ECHA, March 2017 – different compounds have qualitatively similar properties – of the read-across assessment framework i.e. variations in the properties are obsevered among the source substances; the prediction is based on a worst-case approach. Namely, the structurally similar substances as listed below predict the toxicological properties of the target substance MeaTG."

In your justification document, you state for genotoxicity endpoint that "*This document currently focuses on the TGA family. Genotoxicity data of the other subcategories will be added in an update*".

You indicate in the read-across justification document that the prediction is based on a worst-case approach and the structurally similar substances listed in the document predict the toxicological properties of the target substance MeaTG (Monoethanolamine thioglycolate, EC No. 204-815-4). ECHA notes that this does not apply to the Substance because in your justification you refer to a different target substance (MeaTG).

However, ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA notes the following shortcomings with regards to predictions of toxicological properties:

Supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[6]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting information must include information to compare properties of the Substance and source substances.

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substances cause the same type of effects.

In your read-across justification document, you state for genotoxicity endpoint that "*This document currently focuses on the TGA family. Genotoxicity data of the other subcategories will be added in an update*". The Substance belongs to TGA family (thioglycolic acid, its salts and esters). You have not provided any data for the Substance on genotoxicity or any other toxicological endpoint in your dossier or comments to the draft decision. In addition, the source substance belongs to 3-MPA subcategory (3-mercaptopropionic acid and its esters) and the justification document does not yet cover genotoxicity endpoint for this subcategory. Therefore, data set reported in the technical dossier and information provided in your comments on the draft decision does not include relevant, reliable and adequate information for the Substance and of the source substance(s) to support your read-across hypothesis.

In the absence of such information, you have not established that the Substance and of the source substance are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across. 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 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.

Therefore, the sources of information (a) and (b) are substantially unreliable.

B. Validity of the QSAR adaptations relating to the source of information (c) and (d)

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when the following cumulative conditions are met, in particular: results are derived from a QSAR model whose scientific validity has been established.

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

You have provided QSAR predictions for this endpoint, concluding that the Substance is predicted negative for bacterial in vitro mutagenicity (Ames test).

We have assessed the sources of information (c) and (d) you provided and we identified the following issue(s):
In (c), you have not provided sufficient documentation for the QSAR prediction. In particular, you have not included a QMRF and a QPRF in your technical dossier and detailed information is missing. Therefore, ECHA cannot establish whether the model is scientifically valid, whether the Substance and impurity fall within the applicability domain of the model, and whether ther results are adequate for classification and labelling and/or risk assessment.

In addition, in (c) and (d), the scientific validity of the model has not been established, because it does not fulfil the OECD principles for a QSAR model to be considered

scientifically valid (see ECHA Guidance R.6, Section R.6.1.3, and ECHA's Practical guide "How to use and report (Q)SARs", section 3.1), in particular:

- Evaluation of the models in terms of defined endpoint (OECD Principle 1): Data for Ames test are aggregated in YES/NO format without further information for strains and metabolic activation per substance in all models. Thus, the first principle for defined endpoint of the OECD QSAR principles for validity is not met. This means that the scientific validity cannot be established as per Annex XI, 1.3. of REACH.
- Evaluation of the models in terms of unamibiguous algorithm (OECD Principle 2): For both models, the algorithms are not sufficiently transparent to be evaluated. The provided generic descriptions are not sufficient to assess if the models are robust, and can be reliably predictive for scientific and regulatory purposes.
- Evaluation of the models in terms of applicability domain (OECD Principle 3): For both models, domains are arbitrary associated with the model results (depending on the software system); however, without transparent algorithm and underlying training set, it is not possible to assess the definition of the models applicability domains. Provision of similar analogues with the data in this case does not support the target structure (for e.g. among the available analogues, all analogues had missing sulphur group). The uncertainty was assessed as moderate to borderline (with high), structural similarity picked very few chemicals of diverse nature at similarity level of 50% in both Vega and Leadscope systems. Therefore, there was very less structural similarity between the target and analogues. Due to relatively high uncertainty and lack of sufficient number of similar analogues from the QSAR training sets, the models could not be considered any further.

Therefore, sources of information (c) and (d) are substantially unreliable.

Consequently, sources of information (a) to (d) provide information on gene mutation in bacteria but they are not reliable as indicated above. Accordingly, it is not possible to conclude, based on any source information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 471 study. Therefore, your adaptation is rejected.

In your comments on the draft decision, you stated that you fully agree with ECHA about the listed issues. However, you do not see any value of having a new OECD TG 471 test based on the following reasons:

- The Substance is used as a reducing agent in cosmetic formulation and the strains *S. typhimurium TA102* or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) are detecting oxidizing mutagens. Therefore, the outcome of the test can be predicted to be negative for e.g. TA102 based on chemical reactivity.
- Looking at all test results regarding genotoxicity, even in case of a positive result as a worst-case prediction, the overall conclusion will not change. The overall assessment of the test battery will remain the same: not genotoxic.
- The negative prediction of the outcome with e.g. TA102 is confirmed for the whole group of SH-bearing compounds produced and REACH-registered by you.

Instead of experimental testing with e.g. TA102, you suggest summarizing all available data regarding the information requirement for genotoxicity based on ECHA's Read-Across Assessment Framework. At the end, you expect to conclude that a risk for genotoxicity for this group of chemicals cannot be identified at all. You claim that newly conducted tests will have a negative outcome regarding the induction of gene mutations (mutagenicity).

As explained above you have not provided reliable information to confirm negative prediction for the endpoint of *in vitro* gene mutation in bacteria, neither in *TA 102* strain nor in any other bacterial strain required to be tested in OECD TG 471 study.

The information provided does not enable appropriate evaluation of mutagenicity of the Substance in bacteria as required by OECD TG 471. Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

2. Growth inhibition study aquatic plants

A growth inhibition study in aquatic plants is a standard information requirement in Annex VII to REACH.

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Annex XI, Section 1.2.

You have provided the following sources of information:

a) a toxicity study to aquatic algae and cyanobacteria by [redacted] (2009) performed according to EU Method C.3/OECD TG 201 with the source substance Reaction mass of 1,2-hydroxy-3-propylmercaptoacetate and glycerol and 2-hydroxy-1,3-propanediyl bis(mercaptoacetate) or GMT, EC No. 901-060-9;
b) a toxicity study to aquatic algae and cyanobacteria by [redacted] (2005a) performed according to OECD TG 201 with Diammonium dithiodiglycolate or DADTDG, EC No. 269-323-4 (CAS No. 68223-93-8);
c) a toxicity study to aquatic algae and cyanobacteria by [redacted] (2005b) performed according to OECD TG 201 with (2-hydroxyethyl)ammonium thioglycolate or MeaTG, EC No. 269-323-4 (CAS No. 126-97-6);
d) a toxicity study to aquatic algae and cyanobacteria by [redacted] (2001) performed according to EU Method C.3/OECD TG 201 with the source substance Thioglycolic acid or TGA, EC No. 200-677-4 (CAS No. 68-11-1);
e) a toxicity study to aquatic algae and cyanobacteria by [redacted] (1999) performed according to OECD TG 201 with the source substance 2-ethylhexyl thioglycolate or EHTG , EC No. 231-626-4 (CAS No. 7659-86-1);
f) a toxicity study to aquatic algae and cyanobacteria by [redacted] (2009) performed according to EU Method C.3/OECD TG 201 with the source substance Pentaerythritol tetrakis(3-mercaptopropionate) or PETMP, EC No. 231-472-8 (CAS No. 7575-23-7);

In addition, in order to justify the use of sources of information relating to other substances, you have provided various read-across justification documents including:

i. a reference to a publication by [redacted]. (2019) on the environmental hazard and risk assessment of thiochemicals (Chemosphere 214 (2019) 480-490);
ii. a category read-across justification document entitled "[redacted]";
iii. an internal report by [redacted] entitled "[redacted]".

Finally, you have provided two QSAR prediction reports based on the OECD Toolbox . You have not provided any literature reference to any specific study report(s) for these QSAR

predictions

Section 1. above already describes the nature and conditions of a weight or evidence adaptation. In particular, Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You have not included a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

a) Assessment of the relevance of the information provided in support of your adaptation

To fulfil the information requirement, normally a study performed according to OECD TG 201 must be provided. The key parameter to be covered is the concentration in the test substance leading to a 50 % inhibition of growth at the end of the test. Growth must be expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period.

The experimental data as well as the QSAR predictions included in your dossier are considered relevant are they intend to investigate the key parameter of they OECD TG 201.

b) Assessment of the reliability of the information provided in support of your adaptation

i) Reliability of the experimental data provided in your dossier

To comply with this information requirement, an OECD TG 201 study must fulfil the validity criteria and cover the key parameters of the corresponding TG (Article 13(3) of REACH) and the requirements of GD 23 if the substance is difficult to test, which include (among others):

- the measurement of inhibition of growth, expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period;
- the use of an initial biomass concentration following the specifications of the technical guideline;
- biomass data for each flask at each measuring point and method for measuring biomass
- results of analyses to determine the concentration of the test substance in the test vessels. Where concentrations do not remain within 80-120 % of nominal, analysis must be conducted at 24 hour intervals on all test concentrations in order to better define loss of the test substance.

On study (b)above:

- You specify the final test was conducted at a single nominal concentration of 100 mg/L (as test material). You indicate that the test material has an active ingredient content of 45.8%. You have not provided information on the presence of impurities and/or co-solvent (if any);
- You have not reported any information on the stability of the exposure to the active substance during the test;

- You report that the study was conducted on *Desmodesmus subspicatus* and that the initial cell density was 10^4 cells per mL;
- You have not provided biomass data for each flask at each measuring point.

On study (c) above:

- You specify the final test was conducted at a single nominal concentration of 100 mg/L (as test material). You indicate that the test material has an active ingredient content of 45.8%. You report that the purity of the active substance was 83.7% and you have not provided qualitative and quantitative information on impurities.
- You state that a "*decline in measured test concentrations*" was observed but you have not reported any measurement of exposure concentrations during the test;
- You report that the study was conducted on *Desmodesmus subspicatus* and that the initial cell density was 10^4 cells per mL;
- You have not provided biomass data for each flask at each measuring point.

On study (d) above:

- You report that the mean recovery of the test substance after 72h was 41%. You have not reported the results of test substances quantification in all test concentrations at 24 hour intervals;
- You have not provided biomass data for each flask at each measuring point.

On study (e) above:

- You state that a solution was prepared by adding 100 mg of substance in 1 L of water. This solution was agitated vigorously for 24 and filtered to obtain the saturated solution. This solution was tested at 0, 1.94, 4.2, 9.4, 20.6, 45.4 and 100% v/v.
- Analytical monitoring of exposure concentration was conducted at t=0h and t=72h in the absence of algae. At t=0h, the test substance concentration was below the limit of quantification (LOQ) of the analytical methods (i.e. 0.172 mg/L) at nominal concentrations of 4.2% v/v or below. At t=72h, the test substance concentrations were below the LOQ at the nominal concentration of 20.6% v/v or below. You have not reported the results of test substance quantification in all test concentrations at 24 hour intervals;
- You have not provided biomass data for each flask at each measuring point.

On study (f) above:

- You state that the test was conducted at a single concentration of 0.65 mg/L (measured) corresponding to the highest achievable dissolved concentration for the test substance. You further specify that "*the test preparations at 24 hours showed a decline in measured test material concentrations to 0.11 mg/L*". You have not reported the results of test substance quantification at 24 hour intervals over the entire exposure period;
- You have not provided biomass data for each flask at each measuring point.

For studies (b) and (c) you have not provided adequate information on the identity of the test substance including an unambiguous estimate of the content in active ingredient and of the presence of impurities. For study (b) to (f) above, you have not provided adequate information to appropriately characterise exposure throughout the exposure period. In addition, for these studies, you have not provided biomass data for each flask at each measuring point and therefore it is not possible to verify that the validity criteria of the OECD TG 201 were fulfilled. Furthermore, for studies (b) and (c), the initial cell density was two times higher than the value specified for *Desmodesmus subspicatus* in the OECD TG 201 and this may have impacted the sensitivity of the test.

Hence, with the exception of study (a) above, none of the studies from your dossier provides an reliable coverage of the key parameters of the OECD TG 201 and therefore cannot be considered as a reliable source of information to support your weight-of-evidence adaptation.

ii) 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 (addressed under 'Scope of the grouping'). Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

In your registration dossier you have formed a group (category) of 'thioglycolates'. You have provided a read-across justification document in Section 6.1.5 of your IUCLID dossier.

For the purpose of this decision, the following abbreviations are used for the group members:
[1] Thioglycolic acid or TGA (EC No. 200-677-4);
[2] Diammonium dithiodiglycolate or DADTDG (EC No. 269-323-4);
[3] Ammonium thioglycolate or ATG (EC No. 226-540-9);
[4] (2-hydroxyethyl)ammonium thioglycolate or MeaTG (EC No. 269-323-4);
[5] Sodium thioglycolate or NaTG (EC No. 206-696-4);
[6] Potassium thioglycolate or KTG (EC No. 252-038-4);
[7] Calcium thioglycolate or CaTG (EC No. 249-881-5);
[8] Butyl thioglycolate or BuTG (EC No. 233-156-5);
[9] Isotridecyl thioglycolate or $iC_{13}TG$ (EC No. 260-730-2);
[10] Myristyl/lauryl thioglycolate or $nC_{14\text{-}12}TG$ (EC No. 223-138-5);
[11] 2-ethylhexyl thioglycolate or EHTG (EC No. 231-626-4);
[12] Isooctyl thioglycolate or iOTG (EC No. 223-138-5);
[13] Glyceryl monothioglycolate or GMT (EC No. 250-264-8);
[14] Glyceryl dithioglycolate or GDT (EC No. 264-383-8);
[15] glycol dimercaptoacetate or GDMA (EC No. 204-653-4);
[16] trimethylolpropane tris(mercaptoacetate) or TMPMA (EC No. 233-480-7); and
[17] pentaerythritol tetrakis(mercaptoacetate) or PETMA, i.e. the Substance (EC No. 233-482-8).

You provide the following reasoning for the grouping the substances:
- The group members have similar chemical structure and functional groups: you state that the group members are structurally similar and includes free thioglycolic acid, thioglycolate salts, and esters and di- or multimers of thioglycolate derivates. They share "*the same functional sulfur groups within the respective groups of*

thiochemicals";

- Impurities and by-products are expected to be similar: you state that "*The major degradation processes* [...] *are the oxidation of free SH groups to disulfide and ester hydrolysis*". You further explain that "*Another group of impurities are the so-called thioglycolides or thiopropionides* [which] *are polycondensation products* [formed] *in an esterification reaction* [when] *the respective mercaptocarboxylic acids is used in excess. The free SH group of the resulting ester can react again with another molecule of the respective mercaptocarboxylic acid*" Finally you state that "*Depending on the degree of purity, the impurities described above were also tested in the experimental studies, so that in principle it can be assumed that the influence on the extrapolations made here should be of negligible nature*".

You define the applicability domain of the category as follows:
- The category includes "*free acid and salts*";
- It also includes "*Esters* [with] *R1 = linear and branched alkyl chains partly with OH*";
- Finally it includes "*Di(multi)mere with 0-4 free SH*";
- The number of carbon atoms ranges from 2 to 16.

You have provided the following reasoning for the prediction of aquatic toxicity:
- The group members have similar chemical structure leading to similar reactivity: you state that "*Due to the same functional sulfur groups within the respective groups of thiochemicals, a similar reactivity (toxicodynamics) can be assumed within the groups*".
- The group members have similar reactivity leading to similar ecotoxicological properties: you state that "*the substances are toxic because of their functional sulfur groups which can react with biogenic structures*" and that their toxicity "*exceed*[s] *the so-called narcotic effect (baseline toxicity)*"
- Differences in ecotoxicological properties are mainly due to difference in chemical structure, reactivity and hydrophobicity: you state that "*the esters are much more toxic than the respective free acids, presumably due to differences in reactivity and hydrophobicity*" and that "*differences in the acute aquatic toxicities [...]dependent on theirs physicochemical properties (toxicokinetics), e.g. the size of the molecules (chain length, molecular weight) or their hydrophobicity (n-octanol / water partition coefficient log KOW)*".
- With regard to uncertainties in the prediction of acute aquatic toxicity within the group, you state the following:
  - "[for] *DADTDG, no estimates are given because, unlike the other TGAs, this substance does not contain a free SH group and therefore the estimates are too uncertain*";
  - "[for] *iC$_{13}$TG and* [...] *nC$_{14\text{-}12}$TG, no estimates are given because these are due to extrapolations outside the range examined, both in terms of chain length and log KOW. are too insecure*".

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted based on an identified trend within the group.

For growth inhibition to aquatic plants, you intend to predict the properties for the category members from information obtained from the following source substances:

- Reaction mass of 1,2-hydroxy-3-propylmercaptoacetate and glycerol and 2-hydroxy-1,3-propanediyl bis(mercaptoacetate) or GMT, EC No. 901-060-9 ([redacted], 2009);
- Diammonium dithiodiglycolate or DADTDG, EC No. 269-323-4 ([redacted], 2005a)
- (2-hydroxyethyl)ammonium thioglycolate or MeaTG, EC No. 269-323-4 ([redacted], 2005b)
- Thioglycolic acid or TGA, EC No. 200-677-4 ([redacted], 2001)
- 2-ethylhexyl thioglycolate or EHTG, EC No. 231-626-4 ([redacted], 1999)
- Pentaerythritol tetrakis(3-mercaptopropionate) or PETMP, EC No. 231-472-8 ([redacted], 2009)

ECHA notes the following shortcomings with regards to predictions of aquatic toxicity:

1) *Absence of read-across documentation for source substance Pentaerythritol tetrakis(3-mercaptopropionate) or PETMP*

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[7]

You have provided a study conducted with Pentaerythritol tetrakis(3-mercaptopropionate) with EC No. 231-472-8 in order to comply with the REACH information requirements. You have not provided documentation as to why this information is relevant for your Substance.

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on this source substance.

2) *Read-across hypothesis contradicted by existing data for source substance Diammonium dithiodiglycolate or DADTDG*

Annex XI, Section 1.5 of the REACH Regulation requires that "*Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group or 'category' of substances*". According to the ECHA Guidance[8] "*a demonstration of consistent trends in the behaviour of a group of chemicals is one of the desirable attributes of a chemical category and one of the indicators that a common mechanism for all chemicals is involved*". The observation of a deviation in a trend among some members of a category is a warning sign. An explanation for this deviation in the trend resulting in a contradiction between the similarities in properties claimed in the read-across hypothesis and the observation of different properties needs to be provided and supported by scientific evidence.

[7] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.2

8 ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.2.2, (version 1.0, May 2008)

In your read-across justification document you state that "[for] *DADTDG, no estimates are given because, unlike the other TGAs, this substance does not contain a free SH group and therefore the estimates are too uncertain*". You have provided a toxicity study to aquatic algae and cyanobacteria by Mead & McKenzie (2005a) performed according to OECD TG 201 with DADTDG showing no effects at 100 mg/L (nominal). For the other group members you have reported 72h-ErC50 values ranging from 0.91 to 65 mg test substance/L.

As already explained under issue A. above, most of the supporting studies have deficiencies which impact the reliability of the reported results. However, despite those uncertainties, the available data indicates a deviation in your claimed trend of increasing aquatic toxicity with increasing carbon number for DADTDG. Therefore, you have not demonstrated and justified that the properties of the source substance DADTDG follows the regular pattern claimed in your read-across justification.

3) Data density

According to the ECHA Guidance, one of the factors in determining the robustness of a category is the density and distribution of the available data across the category.[9] To identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available.
Furthermore in larger categories there may be breaks in trends which could affect the reliability of interpolation.[10] To confirm that there are no such breakpoints, adequate and reliable information needs to cover also substances within a range of homologous series.

You have provided toxicity study to aquatic algae and cyanobacteria for five category members (Substances [1], [2], [4], [11] and [13], listed above under 'Scope of grouping') which have a carbon number ranging from 2 to 10. Based on these studies you claim that there is a trend in increasing toxicity (in mmol/L) with increasing carbon number.

As explained under issue i) above (Reliability of the experimental data provided in your dossier), out of these five studies four studies are not providing an adequate coverage of the key parameters foreseen to be investigated in an OECD TG 201 study. Therefore the available dataset does not include adequate data to justify the existence of a regular trend within the category. Furthermore, you have not provided any data on the upper border of the category and it cannot be confirmed that there is no breakpoint in toxicity trend within the given range of carbon number. Therefore, the information provided is not sufficient to conclude that ecotoxicological properties are likely to follow a regular pattern.

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

[9] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.1.5.
[10] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.2.

information supporting your weight-of-evidence adaptation are substantially unreliable.

iii) Qualitative or quantitative structure-activity relationship (QSAR)

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when the following cumulative conditions are met, in particular results must be derived from a QSAR model whose scientific validity has been established.

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

You have provided two QSAR prediction for this endpoint, concluding that the substance has an effect value 0.26 mg/L (based on biomass) or 3.03 mg/L (based on growth rate).

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

The scientific validity of the model has not been established, because it does not fulfil the OECD principles for a QSAR model to be considered scientifically valid (see ECHA Guidance R.6, Section R.6.1.3, and ECHA's Practical guide "How to use and report (Q)SARs", section 3.1), in particular:

- according to OECD Principle 1, a (Q)SAR model must be associated with a defined endpoint;
- according to OECD Principle 3, a (Q)SAR model must be associated with a defined domain of applicability; and
- according to OECD Principle 4, for (Q)SAR validation, a (Q)SAR model must be associated with appropriate measures of goodness-of–fit, robustness and predictivity. In particular, two types of information must be provided: a) the internal performance of a model (as represented by goodness-of-fit and robustness), determined by using a training set; and b) the predictivity of a model, determined by using an appropriate test set.

You have provided QSARs developed using the OECD QSAR Toolbox. The queries defined to retrieve data on toxicity to algae use the following terms: "*EC10 <OR> EC50 <OR> EC90 <OR> NOEC*". Therefore, these QSARs are in breach of the OECD Principle 1 as it is unclear what endpoint the model is supposed to predict.
You have not defined the domain of applicability of either of these models. Therefore, these QSARs are in breach of the OECD Principle 3.
Finally, you report that the internal performance of these models, based on goodness-of–fit estimated of R^2adj = -0.0119 and 0.113, respectively. You have not provided any estimate of the predictivity of the model using an appropriate test set. Therefore, these QSARs are in breach of the OECD Principle 4. We note that the internal performance of these models is very low and, in any case, the predicted value reported by you cannot be considered as reliable.

As explained above, you have not established the scientific validity of the proposed QSAR models. Therefore, sources of information supporting your weight-of-evidence adaptation are substantially unreliable.

As a conclusion, the sources of information you have include in your dossier in support of your weight-of-evidence adaptation provide information on growth inhibition in aquatic plants. However, for the reasons explained above, these sources of information lack essential elements in order to provide a reliable basis to conclude on the toxicity of the Substance to aquatic plants.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular property foreseen to be investigated in an OECD TG 201 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

In your comments on the draft decision, you acknowledge that further data based on OECD TG 201 will be produced and will be used to update your read-across grouping approach. However, we stress that at least all the deficiencies described above have to be resolved for a read-across approach to be considered valid.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[11].

B. Test material

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[12].

[11] https://echa.europa.eu/practical-guides
[12] https://echa.europa.eu/manuals

Appendix C: Procedure

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 03 July 2019.

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 and the deadline.

With reference to your comments, the timeline indicated in the draft decision to provide the information requested is 6 months from the date of adoption of the decision.

In your comments to the draft decision, you requested an extension of the timeline as you intend to improve the read-across approach. Also, you invoke your nature as SME and the fact that read-across/grouping and waiving approaches are complex and therefore you require time to be developed.

However, in your comments you have not indicated any issues (including laboratory capacity) related to the performance of the studies requested in this decision. Therefore, the arguments provided above do not justify your request to extend the timeline and ECHA has not modified the deadline of the decision.

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

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

Appendix D: List of references - ECHA Guidance[13] and other supporting documents

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

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

Read-across assessment framework (RAAF, March 2017)[14]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[14]

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

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

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

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

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

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

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

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

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[15]

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

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Note: Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.