EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 1 June 2021

Addressees
Registrant(s) of JS_203-841-3 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
12/12/2019

Registered substance subject to this decision ("the Substance")
Substance name: 3,3'-thiodi(propionic acid)
EC number: 203-841-3
CAS number: 111-17-1

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 ***6 September 2022***.

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. Skin sensitisation (Annex VII, Section 8.3.; test method:

   - i) *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.) with the Substance; and
   - ii) *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429) with the Substance, in case the *in vitro/in chemico* test methods specified under point i) are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment

B. Information required from all the Registrants subject to Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

Reasons for the request(s) are explained in the following appendices:

- Appendices entitled "Reasons to request information required under Annexes VII to VIII of REACH", respectively.

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 tpa;

- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 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. Skin sensitisation

Skin sensitisation is an information requirement under Annex VII (Section 8.3.). Under Section 8.1., Column 1, the registrants must submit information allowing a conclusion whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and risk assessment, where required.

You have adapted the standard information requirements mentioned above by applying a weight of evidence (WoE) adaptation in accordance with Annex XI, Section 1.2.

In support of your adaptation you have provided the following information:

i. QSAR predictions from the Toolbox, VEGA, Molcode and Toxtree models;
ii. a non guideline *in vivo* guinea pig maximisation study with the Substance derived from a scientific publication (2010);
iii. a non guideline maximisation study in human volunteers with the Substance derived from a scientific publication (2010);
iv. a non guideline photoallerginicity study in human volunteers with the Substance derived from a scientific publication (2010);
v. a review article on the side effects of cosmetic and drugs used in dermatology (1994).

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 WoE adaptation, which would include an assessment of relative weights of the individual pieces of information and the subsequent conclusions drawn.

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.

The weight of evidence must fulfill the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.3 at Annex VII includes similar information that is produced by the OECD TGs 442C, 442D, 442E (*in vitro*) or OECD TG 429 (*in vivo*). At general level, it includes information on the following key elements: A) whether the substance causes skin sensitisation, and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), in case, the substance is considered to be a skin sensitiser.

ECHA has assessed to what extent the sources of information submitted enable a conclusion on the above key elements A) and B) and identified the following deficiencies:

A) Assessment whether the Substance causes skin sensitisation

The sources of information i. to v. provide (partly) relevant information on whether the Substance causes skin sensitisation, but have the following deficiencies affecting their reliability:

1. *Non-acceptable QSAR predictions*

A QSAR prediction can be used to adapt the standard information requirement, if the rules set in Annex XI, Section 1.3 Qualitative or quantitative structure-activity relationship (QSAR) are met.

The following cumulative conditions need to be met:
- Results are derived from a QSAR model whose scientific validity has been established;
- The Substance falls within applicability domain of the QSAR model;
- Adequate and reliable documentation of the applied method is provided; and
- The results are adequate for classification and labelling and/or risk assessment.

You have provided several QSAR predictions (i), concluding that the substance is not sensitising.

However, the reliability of these sources of information is significantly affected by the deficiencies identified below:
- QSAR Toolbox Profilers are not scientifically valid (Q)SAR models to be used as stand-alone because, among other reasons, their predictivity has not been assessed. Specifically for skin sensitisation, this approach also lacks considerations on metabolism. Therefore the results from these Profilers cannot be used to indicate the presence or absence of a certain dangerous property under Annex XI, section 1.3 of REACH. QSAR Toolbox Profilers can be used to identify analogue substances and apply the grouping and read-across approach if the conditions under Annex XI, section 1.5. are fulfilled; or used as supporting information.
- ECHA considers VEGA and Molcode predictions to be outside the applicability domain of the respective models due to the low similarity among the structure of target chemical and the structures used as training set of the models. For this reason, the results cannot be used to indicate the presence or absence of a certain dangerous property under Annex XI, section 1.3 of REACH.
- Toxtree results do not include documentation on the structures used for deriving the alerts (i.e. the training set). Information on metabolism is also missing. Furthermore, it is unclear whether the model takes metabolism into account. Lacking this information, ECHA cannot asses the reliability of this prediction. In the absence of adequate documentation, this information cannot be used to indicate the presence or absence of a certain dangerous property under Annex XI, section 1.3 of REACH.

Based on the above, none of the reported QSAR predictions fulfils the criteria in Annex XI, Section 1.3. Therefore, they cannot be considered a reliable source of information that could contribute to the conclusion on this key element.

2. Reliability of the in vivo and human data provided

You indicated a reliability score of 4 to studies ii. to v. ECHA agrees that these studies are not assignable and therefore unreliable in respect to hazard identification.

In the absence of reliable QSAR predictions and reliable information on *in vivo* or human sensitisation, no conclusion can be drawn on whether the Substance causes skin sensitisation as required by the information requirement.

B) Assessment whether the Substance can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

As the currently available data does not allow to conclude whether the Substance causes skin sensitisation, this key element cannot be assessed.

As a conclusion, sources of information as indicated above provide information on whether the substance causes skin sensitisation but they are not reliable due to missing justification and supporting evidence, as well as lack of reliability of the QSAR predictions and *in vivo* and human data provided.

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 dangerous property foreseen to be investigated by the required studies.

In your comments to the draft decision, you indicate your intention to use a category approach to fulfil this information requirement and that you will provide this information in an update of your registration dossier. The information in your comments is not sufficient for ECHA to make an assessment. In particular, the submitted information does not allow to differentiate the reliability of predictions for skin sensitising analogue substances and non-sensitising analogue substances, since it is not clear whether the predictions take into account all relevant parameters such as metabolism. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro/in chemico* studies (OECD TG 442C, 442D and 442E) are considered suitable. In case *in vitro/in chemico* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study must be performed and the murine local lymph node assay (LLNA) (OEDC TG 429) is considered as the appropriate study.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the in vitro gene mutation test in bacteria and the in vitro cytogenicity test.

For Annex VIII, 8.4.3., you have adapted the standard information requirement mentioned above according to Annex XI, Section 1.3. (Qualitative or quantitative structure-activity relationship (QSAR)) of REACH.

In support of your adaptation you have provided the following information:

i. Six QSAR predictions from the following models in the Danish QSAR Database: MultiCASE CASE Ultra, Leadscope Enterprise and SciMatics SciQSAR models.

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

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:

1. results are derived from a QSAR model whose scientific validity has been established;
2. the substance falls within the applicability domain of the QSAR model;
3. adequate and reliable documentation of the applied method is provided; and
4. the results are adequate for classification and labelling and/or risk assessment.

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 the *in vitro* mammalian cell gene mutation endpoint, concluding that the substance is not mutagenic.

You have not provided sufficient documentation for the QSAR prediction. In particular, you have not included in your technical dossier details regarding the following:

- **applicability domain** of the model: you state that the Danish QSAR Database considers the Substance falling within the applicability domain of the model. However, neither the software nor your documentation provides information that can allow ECHA to confirm this claim.
- **adequacy of the prediction**: from the provided documentation, ECHA cannot assess whether the predicted endpoint matches exactly the REACH standard information requirement for *in vitro* mammalian cell gene mutation. More specifically, reliable information on the source of data for building the models is missing.
- **documentation**: your documentation lacks QPRF details to assess the adequacy and validity of the prediction. Furthermore, you have not provided robust study summaries for the tests whose results form the basis for the prediction.

Therefore, ECHA cannot establish whether the model is scientifically valid and whether the Substance falls within the applicability domain of the model. ECHA can neither establish whether the studies, whose results are the basis for prediction, are reliable. Consequently,

ECHA cannot establish whether the results are adequate for classification and labelling and/or risk assessment.

Based on the above, the adaptation you provided does not fulfil the criteria specified in Annex XI, Section 1.3. and it is therefore rejected.

Your dossier contains valid negative results for both an Ames test and an in vitro cytogenicity study. Therefore, the information requirement is triggered.

In your comments to the draft decision, you indicate your intention to use a category approach for "Mercaptocarboxylic acids, their esters and related compounds" by performing further (higher tier) tests for some key Category members to address the genotoxicity endpoints.

With your comments, you have not provided new supporting (experimental) data to support a read-across adaptation. Furthermore, no details are provided on which genotoxicity tests are foreseen to be performed, and it is not specified whether the Substance will be tested.

ECHA cannot conclude on the reliability of the read-across approach proposed in the comments because the acceptability will depend on the outcome of the proposed studies and the relevance of the supporting information. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

Appendix C: 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[2].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

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 variation in compositions reported by all members of the joint submission,
   - 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 and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals

Appendix D: 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 11 December 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 deadline.

> The timeline indicated in the draft decision to provide the information requested is 12 months from the date of the decision.
>
> In your comments to the draft decision, you requested an unspecified extension of the timeline for providing a read-across adaptation, stating the following: *"Our intention is to constantly improve and optimize our strategy in the next years. We would like to further develop a strategy for a Category Approach: Mercaptocarboxylic acids, their esters and related compounds. This is a long and tedious process and we are glad to have the support from our former consultants working with us during the last registration periods. However, we see a risk not to comply with the timelines set in the draft decisions."*. You also mention difficulties for small size companies compared to bigger companies or large consortia considering their respective resources available.
>
> However, you did not provide any documentation to support your request and did not specify the extra time needed. Furthermore, ECHA observes that the studies you proposed to perform were not requested in the draft decision on the Substance. The present decision does not require you to perform such studies and thereby the imposed deadlines cannot be affected.
>
> On this basis, ECHA has not modified the deadline to provide the information.

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 E: List of references - ECHA Guidance[4] 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)[5]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[5]

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[6]

[4] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[5] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[6] 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 F: 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]
[redacted]	[redacted]	[redacted]

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.