EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 12 May 2021

Addressees
Registrant(s) of JS_561-41-1_[redacted] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
29/06/2020

Registered substance subject to this decision ("the Substance")
Substance name: 4,4'-bis(dimethylamino)-4''-(methylamino)trityl alcohol
EC number: 209-218-2
CAS number: 561-41-1

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 ***17 August 2022***.

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

Many of this type of organic pigments are listed in various national inventories of nanomaterials, such as the French nano-particulate substances reporting system.[1] In the case where the Substance is manufactured and/or imported in the European Union in nanoforms by any addressee of the present decision, the REACH Regulation (as amended by Regulation Commission Regulation (EU) 2018/1881) sets out explicit information requirements for nanoforms of substances. Manufacturers and/or importers of nanoforms must have fulfilled these specific information requirements by 1st January 2020. As far as the registration dossiers currently submitted on the Substance by any addressee of the present decision they do not cover any nanoform. Any incompliances identified in the present decision on the Substance relate only to information required on non-nanoforms.

Based on the above, the requested information in this present decision must be generated using exclusively non-nanoforms of the Substance.

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

1. Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105)

2. Partition coefficient n-octanol/water (Annex VII, Section 7.8.; using an appropriate test method)

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

4. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test

[1] "*Dispositif de déclaration des substances à l'état nanoparticulaire* », Decree 2012-232 of French *Conseil d'Etat* of 17 February 2012.

method: EU C.2./OECD TG 202)

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

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

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

4. Adsorption/ desorption screening (Annex VIII, Section 9.3.1.; test method: OECD TG 106 or OECD TG 121)

5. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

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

- Appendix entitled "Reasons common to several requests";
- 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 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[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[2] 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 Reasons common to several requests

1. Assessment of your read-across approach under Annex XI, Section 1.5.

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

In your dossier:
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Adsorption/ desorption screening (Annex VIII, Section 9.3.1.)

In your comments on the initial draft decision:
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) 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[3] and related documents[4, 5].

A. Predictions for (eco)toxicological properties

You have not provided a read-across justification document.

For the endpoints listed above, you used data from the following source substances:

In your dossier:
- Basic Violet 4 (EC 219-231-5)
- Basic Violet 1 (EC 616-846-4)
- Malachite Green (EC 209-322-8)
- 6-(dimethylamino)-3,3-bis[4-(dimethylamino)phenyl]-1,3-dihydro-2-benzofuran-1-one (EC 216-293-5)

[3] 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

[4] 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)

[5] 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

- 4,4'-(phenylmethylene)bis(N,N-dimethylaniline) (EC 204-961-9)
- Gentian Violet (EC 208-953-6)
- Ferrate(4-), hexakis(cyano-C)-, methylated 4-[(4-aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl]benzenamine copper(2+) salts (EC 235-468-7)
- p,p',p''-tris(diethylamino)trityl alcohol (EC 209-886-5)

Additionally, in your comments to the initial draft decision:

- 3,3-bis (p-dimethylaminophenyl) -6-dimethylaminophthalide (EC 216-293-5).
- [4-[α-[4-(dimethylamino)phenyl]benzylidene]cyclohexa-2,5-dien-1-ylidene]-dimethylammonium acetate (EC 255-288-2)
- [4-[bis[4-(diethylamino)phenyl]methylene]-2,5-cyclohexadien-1-ylidene]-diethylammonium chloride (EC 219-231-5)
- 4-[4,4-bis(dimethylamino)benzhydrylidene]cyclohexa-2,5-dien-1-ylidene]-dimethylammonium chloride (EC 208-953-6).

In your comments, you have provided the following reasoning for the prediction of toxicological properties: *" The following assessment intends to demonstrate that the target and read-across substances covered in this justification have common properties and present comparable environmental fate and toxicological behavior".*

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, and that the properties of your Substance are predicted to be quantitatively equal to those of the source substance.

Attached to your comments on the initial draft decision you submitted a read-across justification document. In your justification document you have indicated that 'Scenario 2' was selected for the analogue approach. You provided the following reasoning for the prediction of (eco)toxicological properties: *"read-across of environmental fate, ecotoxicological and toxicological data from an analogue may be justified on the basis of:*

- *Identifying the read across substances based on common functional groups and further filled with relate mechanistic approaches and finally fine-tuned with structural similarity using the QSAR Toolbox Version 3.4*
- *Common structural alerts or reactivity*
- *Common physico-chemical properties*
- *Likelihood of common breakdown products via biological/degradation processes"*

You conclude that *"the descriptors, various alerts and scenario (for analogue approach) which were taken into consideration for ecotoxicological and toxicological assessment as reported in this RA justification document obtained by using OECD QSAR toolbox v.3.4 of the target substance and source substances (i.e., read across analogues) were evaluated to be similar and therefore justified and appropriate".*

As the analogues are used as source substances to predict the property of the Substance, we understand that you have adapted the standard information requirements under Annex XI, Section 1.5 to REACH (grouping and read-across). Based on the above, you used the QSAR Toolbox for the identification of analogues and use information on these analogues to 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(s).

Furthermore, the documentation of the studies provided in your comments on the initial draft decision do not cover sufficient information to make an independent assessment of the study as indicated under the endpoint sections in the below Appendices.

ECHA notes the following shortcomings with regards to prediction of (eco)toxicological properties.

Read-across documentation

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).[6]

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. In your dossier, 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 the source substance(s).

In your comments on the initial draft decision you provided a read across justification but with shortcomings identified in this Appendix.

Missing supporting information to compare properties of the substances

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*"[7]. 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 bridging studies to compare properties of the Substance and source substances.

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 types of substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

You have provided studies in the dossier and in the comments on the draft decision which have been conducted with source substances.

One study performed with the Substance is included in your dossier for the information requirement In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.). This study is however rejected, as explained in section B.2. of this decision.

For the other information requirements, for which you have submitted a read-across adaptation, you have not provided studies that were conducted with the Substance.

Therefore, there is no endpoint-specific information (bridging studies) available to compare properties of the source substances with those of the target substance. The data set reported

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1
[7] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

in the technical dossier and with the 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(s) are likely to have similar properties. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Test material identity

Annex XI, Section 1.5 states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*".

According to the ECHA Guidance, "*the purity and impurity profiles of the substance and the structural analogue need to be assessed*", and "*the extent to which differences in the purity and impurities are likely to influence the overall toxicity needs to be addressed, and where technically possible, excluded*". The purity profile and composition can influence the overall toxicity/properties of the potential category members, including test materials.[8] Therefore, qualitative and quantitative information on the compositions of the test materials should be provided to allow assessment whether the attempted predictions are compromised by the composition and/or impurities.

You do not provide any description of the source substances. Furthermore, for all the studies provided in the technical dossier or in your comments on the initial draft decision that were conducted with these substances, as listed above, no information on the composition of the test material used to generate the source data is provided.

Due to the above deficiency, it is not possible to assess whether the test material is representative for the source substance and thus relevant to the Substance. Therefore, the studies listed above are not adequate for the purpose of classification and labelling and/or risk assessment.

B. 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 substances. 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.

2. Assessment of your weight of evidence adaptation under Annex XI, Section 1.2.

ECHA understands that you have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
2. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
4. Adsorption/ desorption screening (Annex VIII, Section 9.3.1.)
5. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
6. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

[8] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.4.1

Your weight of evidence adaptation raises the same deficiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing the specific standard information requirements in the following appendices.

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.

However, for each relevant information requirement, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

The issue identified below is essential for all the information requirements in which you invoked a weight of evidence.

Reliability of the read across approach

Section 1. of the present Appendix identifies deficiencies of the grouping and read across approach used in your dossier. These findings apply equally to the sources of information relating to analogue substances submitted under your weight of evidence adaptations.

Therefore the studies cannot be regarded as reliable.

Study conducted after 2008 and not GLP compliant

Since 1 June 2008, toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) (Article 13(4) and Article 141(2) of REACH).

The following studies listed below have been performed after 1 August 2008 and not GLP or with GLP compliance not specified

1. Growth inhibition study aquatic plants (2015)
2. Short-term fish studies (2015)

Therefore the studies cannot be regarded as reliable.

These deficiencies are discussed under the respective endpoints.

3. Assessment of your QSAR(s) approach under Annex XI, Section 1.3

ECHA understands that you have adapted the following standard information requirements by applying a QSAR adaptation in accordance with Annex XI, section 1.3:
1. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.2.)
2. Adsorption/ desorption screening (Annex VIII, Section 9.3.1.)

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.

The substance is outside the applicability domain of the model.

ECHA Guidance R.6.1.5.3 specifies that a substance must fall within the applicability domain specified by the model developer.

For ecotoxicological information requirements, the applicability domain of the model you used is defined for Neutral Organics

The Substance used as input for the prediction is not a Neutral organic (since it dissociates in water at pH 5-8).

Therefore, you have not demonstrated that the Substance falls within the applicability domain of the model.

Lack of documentation of the model (QMRF)

The Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3 state that the information specified in or equivalent to the (Q)SAR Model Reporting Format (QMRF) template must be provided to have adequate and reliable documentation of the applied method. For a QMRF this includes:
- The predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model,
- An explicit definition of the algorithm and the descriptor used,
- The definition of applicability domain,
- The goodness-of-fit and robustness of the model, including information on training set and validation statistics.

You have not provided any QMRF document in your technical dossier.

In absence of such information, you have not provided adequate and reliable documentation and therefore ECHA is not in a position to conclude on the validity of the model for prediction of the toxicological properties.

In your comments to the initial draft decision you indicate that there is QSAR Model Reporting Format (QMRF) attached in the dossier which shall be updated within the dossier submitted on REACH IT system shortly. However, there was no such QMRF in the dossier at the time of sending the draft decision. 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).
Lack of documentation of the prediction (QPRF)

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR prediction reporting format (QPRF) template must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

In your dossier or your comments on the initial draft decision, you have not provided information on any of the elements mentioned above. Please note that, in case of QSAR adaptation, a QSAR Prediction Reporting Format (QPRF) must be submitted.

In absence of such information, you have not provided adequate and reliable documentation and therefore ECHA is not in a position to conclude on the validity of the prediction of the toxicological properties.

Further, specific considerations are addressed under the individual information requirements.

Therefore, your adaptations do not comply with the general rules of adaptation as set out in Annex XI, Section 1.3. and your (Q)SAR adaptations are rejected.

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

1. Water solubility

Water solubility is an information requirement under Annex VII to REACH (Section 7.7).
You have provided the following information:

i) Key study (2015) with the shake flask method
ii) Key study (2012) with the shake flask method

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

EU test method A.6 and OECD TG 105 establish the requirements for the data to be reported for a water solubility study. For the flask method, especially the following is required to be reported (among others):

- the results of the preliminary test,
- precise specification of the substance (identity and impurities),
- the individual analytical determinations and the average where more than one value was determined for each flask,
- the pH of each sample,
- the average of the value for the different flasks which were in agreement,
- the test temperature,
- the analytical method employed,
- evidence of any chemical instability of the substance during the test and the method used,
- all information relevant for the interpretation of the results, especially with regard to impurities and physical state of the substance.

You have not reported the parameters listed above for studies (i) and (ii).

In your comments on the initial draft decision you agree to perform the requested study.

Therefore, the provided information does not fulfil the information requirement.

2. Partition coefficient n-octanol/water

Partition coefficient n-octanol/water is a standard information requirement in Annex VII to REACH.

You have provided the following information:

i) Key study (2020), bibliographic source: Chemspider database, Royal Society of Chemistry
ii) Supporting study (2018), LogP: Octanol-water partition coefficient prediction from the OPERA

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

Your dossier contains data for this endpoint (studies (i) and (ii)) that meet Klimisch criterion 4 according to you. ECHA agrees considering the use of secondary literature and the lack of reporting: the robust study summary is missing for the key study (i) and the QPRF-like information is incomplete for the supporting study (ii).

In your comments on the initial draft decision you agree to perform the requested study.

Therefore, the data are not assignable, and it does not fulfil the standard information requirement.

Study design

Guidance for determining appropriate test methods for the partition coefficient n-octanol/water is available in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.1.8 (version 6.0, July 2017).

3. 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.

You have adapted this information requirement by using Grouping of substances and read-across approaches under Annex XI, Section 1.5., and Weight of Evidence under Annex XI, Section 1.2. of REACH.

You have provided the following sources of information to support your adaptations:

Studies in your dossier:

i) *In vitro* gene mutation study in bacteria (2006) with analogue substance Basic Violet 4 (EC 219-231-5).
ii) *In vitro* gene mutation study in bacteria (1981) with analogue substance Basic Violet 1 (EC 616-846-4).

Studies in your comments on the initial draft decision:

iii) *In vitro* gene mutation study in bacteria (2002) with analogue substance 3,3-bis (p-dimethylaminophenyl) -6-dimethylaminophthalide (EC 216-293-5).
iv) *In vitro* gene mutation study in bacteria (2000) with analogue substance [4-[α-[4-(dimethylamino)phenyl]benzylidene]cyclohexa-2,5-dien-1-ylidene]dimethylammonium acetate (EC 255-288-2).

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

A. Read-across

As explained in the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.5. is rejected.

B. Weight of evidence

As explained in Section 2 of the Appendix common to several requests, the weight of evidence must fulfil 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.

To fulfil the information requirement, normally a study according to OECD TG 471 must be provided. The key elements investigated by this test are:

- Detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies; and
- Data provided on 5 bacterial strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The provided studies detect and quantify mutations in bacteria.
However, the provided studies (i and ii) do not include data on the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).

Therefore, the provided studies only provide partly relevant information.

Furthermore, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

In addition, the reliability of the sources of information (i) and (ii) are for this information requirement affected by the following issues:

Testing in accordance with OECD TG 471, requires that the following specifications/ conditions have to be met:

- The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 ml/plate.
- At least 5 doses must be evaluated, in each test condition.

In study (i) the doses were 0.3-100 µg/plate. No justification for dose selection was provided and no information on precipitation or cytotoxicity was reported. In your comments on the initial draft decision you explained that the doses were selected based on cytotoxicity observations in a range-finding study, which addresses the identified deficiencies.

In the reporting of study (ii), it is unclear which, and how many, doses were tested.

Therefore, the provided study (ii) cannot be considered reliable sources of information.

As a conclusion, the sources of information provide information on mutations in bacteria which is only partly relevant, and the information provided is only partly reliable.

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

Information on the study design

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

4. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Annex VII, Section 9.1.1., Column 2 or a general adaptation rule under Annex XI.

You have provided the following information:

i. An adaptation under Annex XI, Section 1.3. In support to your adaptation, you have provided the following information:
   a. Estimation 48 hrs LC50 value of test chemical on aquatic invertebrates by EPI Suite ECOSAR version 1.11.
ii. "this information will be submitted later on substance with 'CAS nr. 561-41-1'"

We have assessed this information and identified the following issues:

A. QSAR calculation

As explained in Section 3 of the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.3. is rejected.

B. Intention to submit data

You intended to submit data on a substance with the CAS nr. 561-41-1. This CAS nr. is actually the Substance itself and you have not submitted so far data further than addressed under section A above.

In your comments on the initial draft decision you agree to perform the requested study.

Study design

The Substance is difficult to test due to its ionic character and the use of the Substance as a dye/ink indicating adsorptive properties. OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solutions.

5. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

You have provided the following information:

i. An adaptation under Annex XI, Section 1.2. In support to your adaptation, you have provided the following information:
   a. Experimental study (2015) non-GLP according to OECD TG 201 with the Substance
ii. "this information will be submitted later on substance with 'CAS nr. 561-41-1'"

We have assessed this information and identified the following issues:

A. Weight of evidence

As explained in Section 2 of the Appendix on Reasons common to several requests, the weight of evidence must fulfil 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.

To fulfil the information requirement, normally a study according to OECD TG 201 must be provided. The key element investigated by this test is growth rate of algal cultures.

All the sources of information you provided investigate this key element. Therefore, they provide information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix common to several requests. ECHA identified additional deficiencies specific to this information requirement,

First, Annex XI, Section 1.2 states that there may be sufficient weight of evidence "from several independent sources of information".
You have only provided one source of information.
Therefore your adaptation is rejected and the information requirement is not fulfilled.

Second, the reliability of the source of information (i) for this information requirement is affected by the following issue:

A. To fulfil the information requirement and comply with OECD TG 201, the following specifications must be met:

- three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;
- one of the two alternative growth medium (i.e. the OECD or the AAP medium) is used. Any deviations from recommended test media must be described and justified;
- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (*i.e.* detection and quantification) and working range must be available. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;
- the concentrations of the test material are measured at least at the beginning and end of the test:
  1) at the highest, and
  2) at the lowest test concentration, and
  3) at a concentration around the expected EC_{50}.

In your registration dossier, you indicated the following on study (i):

Characterisation of exposure
- the number of replicates was 2 in each test concentration
- the test medium is described as Bold's Basal Medium (BBM). You have not provided a justification as why you did not use one of the two alternative growth medium of OECD TG 201
- no analytical monitoring of exposure was conducted with no further justification;

The information provided does not meet the specifications of OECD TG 201.

Third, tests and analyses on the intrinsic properties of substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

The provided study i) was indicated as not being performed according to GLP without further explanation.

Taken together, even if these sources of information provide information on the key element, their reliability is affected so significantly that they cannot be taken into consideration in a

weight of evidence approach.

Therefore, 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 in an OECD TG 201 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

C. Intention to submit data

You intended to submit data on a substance with the CAS nr. 561-41-1. This CAS nr. is actually the Substance itself and you have not submitted so far data further than addressed under section A above.

In your comments on the initial draft decision you agree to perform the requested study.

Study design

OECD TG 201 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.4.

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

1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have adapted this information requirement by using Grouping of substances and read-across approaches under Annex XI, Section 1.5., and Weight of Evidence under Annex XI, Section 1.2 of REACH.

You have provided the following sources of information:

Studies in your dossier:

i) Non-guideline study of chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells (1979) with analogue substance Malachite green (EC 209-322-8)
ii) Chromosome aberration study according to OECD TG 473 (2002) with analogue substance 6-(dimethylamino)-3,3-bis[4-(dimethylamino)phenyl]-1,3-dihydro-2-benzofuran-1-one (EC 216-293-5).

Studies in your comments on the initial draft decision:

iii) Chromosome aberration study according to OECD TG 473 (1999) with analogue substance [4-[bis[4-(diethylamino)phenyl]methylene]-2,5-cyclohexadien-1-ylidene]diethylammonium chloride (EC 219-231-5)
iv) Non-guideline study of chromosomal aberrations in cultured Chinese hamster V79 cells (1979) with analogue substance [4-[4,4-bis(dimethylamino)-benzhydrylidene]cyclohexa-2,5-dien-1-ylidene]dimethylammonium chloride (EC 208-953-6)
v) Non-guideline in vivo study of sister chromatid exchange and chromosomal aberration in chicken embryo with analogue substance [4-[4,4-bis-(dimethylamino)benzhydrylidene]cyclohexa-2,5-dien-1-ylidene]-dimethylammonium chloride (EC 208-953-6)
vi) Non-guideline in vivo study of chromosomal aberration in bone marrow cells with analogue substance [4-[4,4-bis(dimethylamino)benzhydrylidene]-cyclohexa-2,5-dien-1-ylidene]dimethylammonium chloride (EC: 208-953-6).

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

A. Read-across

As explained in the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.5. is rejected.

B. Weight of evidence

As explained in Section 2 of the Appendix common to several requests, the weight of evidence adaptation must fulfil 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.

To fulfil the information requirement, normally a study according to OECD TG 473/487 must be provided. The key element investigated by this test is cytogenicity in mammalian cells.

The provided sources of information investigate cytogenicity in mammalian cells. Therefore, they provide relevant information that would contribute to the conclusion on this key element.

However, the reliability of the sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

In addition, the reliability of the source of information (i) for this information requirement is affected by the following issue:

The conditions of these test guidelines include:

- The maximum concentration tested must induce 55+5% of cytotoxicity compared to the negative control, or lead to precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
- At least 3 concentrations must be evaluated, in each test condition.

In source study (i) only one very low dose (20 µM) was tested, without any justification for the dose selection.

As discussed further below, the information in your comments is not sufficient for ECHA to make an independent assessment. 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).

In the brief description of studies included in your comments, you did not provide any justification for the selection of doses in studies iv), and vi) (highest doses 20 µg/mL and 40 µg/mL, respectively). In addition, only two test concentrations were used in study iv).

Therefore, the provided studies cannot be considered a reliable source of information.

Conclusion

As a conclusion, the sources of information provide information on cytogenicity in mammalian cells but the information provided is not reliable.

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

Information on the study design

To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

2. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

i. Triggering of the study

Your dossier contains an adaptation for an *in vitro* gene mutation study in bacteria, and an adaptation for an in vitro cytogenicity study in mammalian cells or *in vitro* micronucleus study.

The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in section 1 of Appendix A and section 1 of this Appendix B.

The result of the requests for information in section 2 of Appendix A and section 1 of this Appendix B will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

ii. Assessment of information provided

You have provided the following sources of information.

Study in your dossier:

i) *In vitro* mammalian cell gene mutation study (OECD TG 476; 2015) with the Substance.

Studies in your comments on the initial draft decision:

ii) Mouse lymphoma mutagenicity study (comparable to OECD TG 490) with analogue substance [4-[bis[4-(diethylamino)phenyl]methylene]-2,5-cyclohexadien-1-ylidene]diethylammonium chloride (EC 219-231-5)
iii) Mammalian cell mutagenicity assay with analogue substance, [4-[4,4'-bis(dimethylamino)benzhydrylidene]cyclohexa-2,5-dien-1-ylidene]dimethyl-ammonium chloride (Basic violet 3, EC 208-953-6).

In your comments on the initial draft decision you explain that you wish to adapt this information requirement according to Annex XI, Section 1.5. (Grouping of substances and read-across approaches) and under Annex XI, Section 1.2. (Weight of Evidence, using the studies included in your comments).

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

To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490[9]. The key element(s) of these test guidelines include:

a) The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or lead to the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

Assessment of data in your dossier

The reported data for the study you have provided in your dossier (study i) do not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL (as the highest dose was reported as 10 µM), or that induced 80-90% of cytotoxicity compared to the negative control, or lead to precipitation of the tested substance

[9] ECHA Guidance R.7a, Table R.7.7-2, p.557

b) data on the cytotoxicity and the mutation frequency for the treated and control cultures.

The information provided does not cover key elements required by OECD TG 476/490.

Assessment of data in your comments

A. Read-across

As explained in the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.5. is rejected.

B. Weight of evidence

As explained in Section 2 of the Appendix common to several requests, the weight of evidence adaptation must fulfil 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.

To fulfil the information requirement, normally a study according to OECD TG 476/490 must be provided. The key element investigated by this test is gene mutation in mammalian cells.

The provided sources of information investigate gene mutation in mammalian cells. Therefore, they provide relevant information that would contribute to the conclusion on this key element.

However, the reliability of the sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

As a conclusion, the sources of information provide information on in vitro gene mutation study in mammalian cells but the information provided is not reliable.

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

Conclusion

The information requirement is not fulfilled.

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide negative results.

Information on the study design

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.

3. Screening for reproductive/developmental toxicity

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 (Section 8.7.1), 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 the standard information requirement mentioned above according to Annex XI, Section 1.5 (grouping of substances and read-across) of REACH and Weight of Evidence under Annex XI, Section 1.2 of REACH.

You have provided the following sources of information:

i) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422; 2011) with analogue substance C.I. Basic Violet 1 (EC 616-846-4)
ii) Developmental toxicity study (similar to OECD TG 414; 2011) with analogue substance 4,4'-(phenylmethylene)bis(N,N-dimethylaniline) (EC 204-961-9)
iii) Three-generation reproductive toxicity test (2004) with analogue substance Gentian Violet (EC 208-953-6)
iv) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422; 2009) with analogue substance 1H-Pyrrole-2,5-dione, 1,1'-(methylenedi-4,1-phenylene)bis- (EC 237-163-4)

ECHA has assessed this information and identified the following issue(s):

A. Read-across

As explained in the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.5. is rejected.

B. Weight of evidence

As explained in Section 2 of the Appendix common to several requests, the weight of evidence adaptation must fulfil 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 8.7.3 at Annex VIII includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

The provided sources of information (i, iii, iv) investigate all three key elements. Source study (ii) provides limited information on key elements 2) and 3). Therefore, they provide relevant information that would contribute to the conclusion on them.

However, the reliability of the sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

Furthermore, the reliability of these sources of information is significantly affected by the following deficiencies:

To be considered compliant and to generate information concerning the effects of the Substance on male and female reproductive performance, the study has to meet the requirements of EU B.63/OECD TG 421 or EU B.64/OECD TG 422. The criteria of the test guideline include:

- Highest dose level should aim to induce toxic effects
- At least 10 male and 12-13 female animals for each test and control group

- Dosing of the Substance for a minimum of four weeks for males and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation
- Examination of parameters for sexual function and fertility such as parturition, lactation and weight and histopathology of reproductive organs and tissues.

In source studies (i) and (iv) females were only exposed only until day 4 of lactation. In source study (ii) females were only exposed during gestation days 6-15. Therefore the studies (i, ii and iv) do not have a required exposure duration.

Source study (ii) did not include exposure of males. In studies (i) and (iv), the high-dose male groups consisted only of 7 male rats. The statistical power of the information provided in these studies is not sufficient because it does not fulfil the criterion of at least 10 male and 12-13 female animals for each test group.

In source study (ii) investigations for parameters for sexual function and fertility such as parturition, lactation and weight and histopathology of reproductive organs and tissues have not been performed as required in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

In addition, source study iii) has been given a reliability score of 4 by you (not assignable), with limited reporting and ECHA agrees that this source study is not reliable.

Therefore, the provided studies cannot be considered reliable sources of information.

As a conclusion, sources of information as indicated above, provide information on sexual function and fertility, toxicity to offspring, and systemic toxicity but the information provided is not reliable.

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

In your comments on the initial draft decision you explain that "By on weight of evidence, the registered substance is regarded to be classified as "H361d: suspected of damaging fertility or the unborn child". Conducting an OECD 421 study the registered substance is not considered to be justifiable for animal welfare reasons due to the above classification and the available data on reproductive toxicity for read across analogues".

According to Annex VIII, Section 8.7., Column 2, second paragraph, the study does not need to be conducted if the substance meets the criteria for classification as toxic for reproduction category 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment. However, testing for developmental toxicity must be considered.

Classification as Repr. 2 (H361d) is not a valid adaptation possibility according to Annex VIII, 8.7., Column 2. Furthermore, as explained above, your weight of evidence adaptation is rejected.

Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[10] administration of the Substance.

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

4. Adsorption/ desorption screening

Adsorption/desorption screening is an information requirement under Annex VIII to REACH (Section 9.3.1.).

You have adapted this information requirement by using Grouping of substances and read-across approaches under Annex XI, Section 1.5., Weight of Evidence under Annex XI, Section 1.2. and Qualitative or Quantitative structure-activity relationship ((Q)SAR) under Annex XI, Section 1.3. of REACH.

You have provided the following sources of information:

i) EPI suite KOCWIN Program (v2.00) as by means of MCI method
ii) Adsorption coefficient (Koc) of test chemical was estimated using Chemspider database (reliability 4)
iii) Adsorption coefficient (Koc) of test chemical was estimated using Scifinder database (reliability 4)
iv) Experimental study (2019) with an analogue substance (EC 235-468-7)
v) Experimental study (2019) with an analogue substance (EC 209-886-5)

We have assessed this information and identified the following issues:

A. Read across

As explained in Section 1 of the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.5. is rejected.

B. Weight of evidence

As explained in Section 2 of the Appendix on Reasons common to several requests, the weight of evidence must fulfil 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.

To fulfil the information requirement, normally a study according to OECD TG 106 or 121 must be provided. The key element investigated by this test is the adsorption/desorption behaviour of the substance on soil.

All the sources of information you provided investigate this key element. Therefore, they provide information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix common to several requests.

In addition, the reliability of sources of information (ii) and (iii) is significantly affected for the following reason: According to you, these sources of information meet Klimisch criterion 4'. ECHA agrees considering the use of secondary literature and the lack of reporting without further justification.

Taken together, even if these sources of information provide information on the key element, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

Therefore, 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 in an OECD TG 106 or OECD TG 121 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

C. QSAR calculations

As explained in Section 3 of the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.3. is rejected.

In your comment on the initial draft decision you stated that the databases used for predicting the adsorption coefficient (Koc) of the test chemical (sources (ii) and (iii)) fulfil the following cumulative criteria:

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

However you have not provided any evidence in support of this statement.

On the basis of the above, the information requirement is not fulfilled.

In your comments on the initial draft decision, you indicate if ECHA rejects your weight of evidence, you agree to perform the requested study.

Study design

Considering the properties of the Substance (sparingly soluble particles), the Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) (test method: OECD TG 121) or alternatively the Adsorption/Desorption Using a Batch Equilibrium Method (test method: OECD TG 106) are the most appropriate method to fulfil the information requirement for the Substance.

5. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

You have provided the following information:

i) An adaptation under Annex XI, Section 1.2. In support to your adaptation, you have provided the following information:
   a. Experimental study (2015) non-GLP according to a OECD TG 203 with the registered substance

ii) "this information will be submitted later on substance with 'CAS no. 561-41-1'"

ECHA assessed this information and identified the following issues:

A. Weight of evidence

As explained in Section 2 of the Appendix on Reasons common to several requests, the weight of evidence must fulfil 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.

To fulfil the information requirement, normally a study according to OECD TG 203 must be provided. The key element investigated by this test is the concentration of the test material

leading to the mortality of 50% of the juvenile fish at the end of the test.

All the sources of information you provided investigate this key element. Therefore, they provide information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix common to several requests. ECHA identified additional deficiencies specific to this information requirement,

First, Annex XI, Section 1.2 states that there may be sufficient weight of evidence "from several independent sources of information".

You have only provided one source of information.

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

Second, the reliability of the source of information (i) for this information requirement is affected by the following issue:

To fulfil the information requirement and comply with OECD TG 203, the following specifications must be met:

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;

In your registration dossier, you provided the following on study (i):

- no analytical monitoring of exposure was conducted with no further justification

The information provided does not fulfil the specifications of OECD TG 203.

Third, tests and analyses on the intrinsic properties of substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

The provided study i) was indicated as not being performed according to GLP without further explanation.

Taken together, even if these sources of information provide information on the key element, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

Therefore, 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 in an OECD TG 201 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

D. Intention to submit data

You intended to submit data on a substance with the CAS nr. 561-41-1. This CAS nr. is actually the Substance itself and you have not submitted so far data further than addressed under section A above.

In your comments on the draft decision you agree to perform the requested study.

Study design

OECD TG 203 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.4.

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[11].

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[12].

C. Analytical monitoring

For ecotoxicological information requirements (requests A.4., A.5. and B.5.):

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

- You must select an analytical method that is able to distinguish to the extent technically feasible the Substance and the dissociation products in solution. Otherwise, it is not possible to relate the observed effects to the Substance itself considering that the Substance in environmental pH (5-8), will be mostly dissociated and highly ionisable.
- For the same reason, you must provide a description on the analytical method used, monitor the test concentration(s) to the extent technically feasible, indicate what has been monitored and on which chemical species the effect concentrations are based.

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 13 February 2020.

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

ECHA took into account your comments 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 E: 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 F: Addressees of this decision and their corresponding information requirements

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]
[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.