~~Confidential~~

Helsinki, 24 June 2021

Addressees
Registrant(s) of KK Tartrate as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
30/05/2018

Registered substance subject to this decision ("the Substance")
Substance name: Dipotassium tartrate
EC number: 213-067-8
CAS number: 921-53-9

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 in A.1., A.2., and B.2. below by **29 September 2022** and the other information listed below by **2 April 2024**.

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. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

2. 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. 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

2. 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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 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". 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 on Reasons common to several requests

0. Category and read-across proposed in the comment on the draft decision

For the aquatic toxicity information requirements requested in the present draft decision, in your comments you propose grouping the following substances in the "Tartaric acid and its salts" category and applying a read-across approach in accordance with Annex XI, Section 1.5 :
- tartaric acid (EC 201-766-0);
- sodium potassium tartrate (EC 206-156-8);
- potassium hydrogen tartrate (EC 212-769-1);
- dipotassium tartrate (EC 213-067-8); and
- calcium tartrate (EC 221-621-5).

You propose to report in the registration dossier results of the short-term toxicity study with aquatic invertebrates and of the growth inhibition study with aquatic plants with calcium tartrate which are available in the registration dossier of that substance.

Moreover, in your comments on the draft decision you propose to perform long-term toxicity testing on fish with one of the category members and to report this information in the registration dossier. You intend to use results of the long-term toxicity testing on fish as justification for an adaptation of short-term toxicity testing on fish.

ECHA considers that the proposed read-across approach for the aquatic toxicity information requests is plausible and could fulfil the information gaps as long as reliable studies with member(s) of the category will be reported in the registration dossier and for the aquatic toxicity studies the molecular weight of the counter-ion of the source substance(s) is considered:
- for the selection of the maximum test concentration, in order to ensure that the test concentration of the common tartaric acid anion relevant (i.e. expected to be present when maximum concentration of the target substance as required by the test guideline would be present in the test solution) for each of the target substance(s) (i.e. category members) has been reached in the test with the source substance(s); and
- for the estimation of aquatic toxicity effect concentration for the target substance(s).

The quality of the aquatic toxicity tests will be evaluated after the expiry of the deadline set out in the draft decision according to Article 42 of the REACH Regulation.

1. Assessment of your Weight of Evidence adaptation under Annex XI, Section 1.2.

In your dossier you have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Furthermore, in your comments on the initial draft decision you provided the following information under your title "Comments on reproductive toxicity requests":

- "*Therefore, the Addressees invoke EFSA risk assessment as adaptation under Annex XI to claim that further toxicological testing for reproductive and developmental effects is scientifically unjustified for all the substances in the Category and ask ECHA to consider this issue. Therefore, the Addressees invoke adaptation of information*

requirements according to Annex XI and claim that further toxicological testing for reproductive and developmental effects is scientifically unjustified for all the substances in the Category, considering the results of the assessment performed by EFSA. The Addressees ask ECHA to consider this issue".

- "*information requirements in this specific case can be deemed fulfilled*"; specifically you raised the following:
    - *"ADME data show lower internal exposure to tartaric acid in humans compared to rats"*
    - *"tartrate is not metabolised to oxalate"*
    - *"in available studies, no maternal or developmental effects were reported at the highest dose tested"*
    - *"according to EFSA Panel's review, no studies for reproductive toxicity were available; however, no histopathological findings were reported in testes, ovaries and uterus in various studies"*
    - *"in mice given up to 2150 mg/L (+) tartaric acid/kg bw per day by gavage for 5 days, no statistically significant differences in the frequency of 'cell aberration' in primary spermatocytes were observed in the treated groups compared to the negative control groups"*
    - *"the EFSA Panel considered that monosodium L(+)-tartrate was not carcinogenic and identified an NOAEL of 3100 mg monosodium tartrate/kg bw per day, the highest dose tested".*

Your weight of evidence adaptation raises the same decifiencies 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 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.

In relation to information you submitted referring to risk assessment performed by EFSA, note that an EFSA finding that there is no risk incurred by the dietary exposure of consumers to a substance does not mean that an overall analysis of the intrinsic properties of the substance has taken place as required under the testing annexes of the REACH Regulation.

QSAR predictions rejected

Section 2 of the present Appendix identifies deficiencies of the information based on application of (quantitative) structure-activity relationships (QSAR) submitted under your weight of evidence adaptations.

Conclusion

Your weight of evidence approach has deficiencies that are specific for these information requirements individually. The specific deficiencies are set out under the information requirement concerned in the Appendices below.

2. Assessment of (quantitative) structure-activity relationships estimations

You have provided information based on application of (quantitative) structure-activity relationships (QSAR) as supporting studies for the following standard information requirements:

1. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
2. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

In your comments on the draft decision you have provided predictions by Organic Module Evaluation (ECHA understands by ECOSAR), Vega software and by Consensus for the above listed information requirements. Furthermore, you have provided predictions for Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.) by Vega software and by Organic Module Evaluation (ECHA understands by ECOSAR).

We understand that the QSAR information for human health, which you have provided in your comments on the initial draft decision, relates to the following standard information requirement:

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

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

(i) Information on aquatic toxicity in your dossier and comments on the draft decision

Information generated by application of various QSARs applied by you 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 1.3. states that results obtained from valid QSAR models may be used instead of testing when several 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.

You have provided QSAR predictions by VegaNIC v.1.0.8 and by T.E.S.T. v.4.1 for the aquatic toxicity endpoints listed above in the registration dossier in order to comply with the REACH information requirements.

You have provided in the dossier documentation supporting applied models.

We have assessed this information and identified the following issues:

Applicability domain of the VegaNIC v.1.0.8 toxicity models for Daphnia and fish and adequacy for classification and labelling and/or risk assessment

ECHA Guidance R.6. explains that, in order for a QSAR result to be adequate for classification and labelling and/or risk assessment, the following conditions must be fulfilled:

- the estimate should be generated by a valid (relevant and reliable) model;
- the model should be applicable to the chemical of interest with the necessary level of reliability;
- the model endpoint should be relevant for the regulatory purpose.

The Guidance R.6 further notes that if a model is applied to a chemical outside its applicability domain, it is possible that the estimated result may be not sufficiently reliable for the purpose. It is therefore important to determine the applicability of the model to the chemical of interest.

You have provided documentation of the *VegaNIC v.1.0.8 toxicity models for Daphnia and fish and documentation of the prediction by these models. However,* the compounds in the training set for both the fish and Daphnia VegaNIC v.1.0.8 toxicity models have significant differences to the predicted substance. E.g. there are no compounds which would include two carboxyl and two hydroxy functional groups, as the predicted substance or some compounds have elements (e.g. nitrogen, phosphorus) and functional groups (e.g. ester) which are not present in the structure of the predicted substance. Furthermore, the document provided for the fish model states: "*only moderately similar compounds with known experimental value in the training set have been found*".

You have not explained why the predicted substance would be within the applicability domain of the VegaNIC v.1.0.8 toxicity models for Daphnia and fish, and why the prediction can be considered adequate for the regulatory purpose, i.e. classification and labelling and/or risk assessment, despite the issue noted.

In absence of such information, you have not established that the model can be used to meet the above listed information requirements.

Inadequate documentation of the model (QMRF) for T.E.S.T. v.4.1, Organic Module Evaluation and Consensus

Under 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., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

You have provided in the dossier document describing the toxicity models for Daphnia

and fish applied without a definition of the applicability domain. Furthermore, you have not included QMRFs for the aquatic toxicity predictions by Organic Module Evaluation and Consensus method provided in your comments on the draft decision.

In absence of such information, ECHA cannot establish that the model can be used to meet above listed information requirements.

Inadequate documentation of the prediction (QPRF) for T.E.S.T. v.4.1, Organic Module Evaluation and Consensus

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) 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.

You have provided in the dossier a QPRF document providing description of predictions of toxicity for Daphnia and fish without information about the relationship between the modelled substance and the defined applicability domain. Furthermore, you have not included QPRFs for the aquatic toxicity predictions by Organic Module Evaluation and Consensus method provided in your comments on the draft decision.

In absence of such information, ECHA cannot establish that the prediction can be used to meet above listed information requirement.

(ii) Adequacy of predictions for the purpose of risk assessment and/or classification and labelling

Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with information available for other related endpoint(s).

In your comments on the draft decision you provided predictions by Vega software for the aquatic toxicity.

Based on the models' reports provided in your comments, these predictions for the Substance used as input are uncertain. More specifically, in the reports of the specific aquatic toxicity models provided in your comments the following issues are noted:

1) "*only moderately similar compounds*" in the training set have been found;

2) "*some similar molecules found […] have experimental values that disagree with the predicted value*";

3) the Substance cannot be classified according to the rules implemented in the model, so "*it is not possible to perform an assessment*";

4) the Substance could be out of the applicability domain of the model;

5) "*the maximum error in prediction of similar molecules[…] has a moderate value*";

6) the Substance is out of the applicability domain of the model;

The following issues cause prediction(s) by the specific model to be uncertain:

- MOA toxicity classification by EPA T.E.S.T. 1.0.0: issues 1 and 2;
- Verhaar classification by TOXTREE 1.0.0: issue 3;
- Fish acute classification by SarPy/IRFMN 1.0.2: issue 1;
- Fish Acute Toxicity by KNN/Read-Across 1.0.0: issues 4 and 5;
- Fish Acute Toxicity by NIC 1.0.0: issues 1, 2 and 4;
- Fish Acute Toxicity by IRFMN 1.0.0: issues 1, 2 and 6;
- Fish Acute Toxicity by IRFMN/Combase 1.0.0: issues 1, 4 and 5 etc.;
- Fish (Fathead Minnow) Acute Toxicity by EPA 1.0.7: issues 1 and 4;
- Fish (Fathead Minnow) Acute Toxicity by KNN/IRFMN 1.1.0: the Substance has both, (double) carboxyl acid and (double) alcohol functional groups with no other functional groups present in the molecule, while the training set contains acids (without alcohols), alcohol (without acids), ester, and alcohols with ester functional group; thus, ECHA considers that there is a lack of sufficiently similar substances in the training set;
- Aquatic invertebrates (*Daphnia magna*) Acute Toxicity by EPA 1.0.7: issues 1 and 6 etc.;
- Aquatic invertebrates (*Daphnia magna*) Acute Toxicity by Demetra 1.0.4: issue 4;
- Aquatic invertebrates (*Daphnia magna*) Acute Toxicity by IRFMN 1.0.0: issues 1 and 4;
- *Daphnia magna* Acute Toxicity model: issues 1 and 6 etc.;
- Algae Acute Toxicity by IRFMN 1.0.0: issues 1 and 4;
- Algae Acute Toxicity by ProtoQSAR/Combase: issues 1 and 4;
- Algae Chronic Toxicity by IRFMN 1.0.0: issues 1, 2 and 4;
- Algae Classification Toxicity by ProtoQSAR/Combase: issue 1.

Furthermore, some of used models provide only qualitative information (e.g. MOA toxicity classification by EPA T.E.S.T. 1.0.0, Verhaar classification by TOXTREE 1.0.0, Algae Classification Toxicity by ProtoQSAR/Combase) and thus does not serve the purpose of filling data gap for an information requirement.

Finally, quantitative predictions of short-term effect concentration for fish by various models

significantly differ (e.g. LC50 of 9.3 mg/l by NIC 1.0.0 and of 534.54 mg/l by IRFM/Combase 1.0.0). You have not further explained which value of short-term effect concentration for fish should be used for the purpose of classification and labelling and/or risk assessment.

Therefore, you have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

(iii) Information for human health in your comments on the initial draft decision

In your comments you do not refer to QSAR adaptations for human health. However, you provided documentation using VEGA reports on:

i. Developmental Toxicity model (CAESAR) 2.1.7
ii. Developmental/ Reproductive Toxicity library (PG) 1.1.0
iii. Estrogen Receptor Relative Binding Affinity model (IRFMN) 1.0.1
iv. Estrogen Receptor-mediated effect (IRFMN/CERAPP) 1.0.0
v. Androgen Receptor-mediated effect (IRFMN/COMPARA) 1.0.0
vi. Thyroid Receptor Alpha effect (NRMEA) 1.0.0, and
vii. Thyroid Receptor Beta effect (NRMEA) 1.0.0.

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

Modelled endpoint not well defined

Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. The first OECD principle requires the endpoint of a (Q)SAR model to be well defined. ECHA Guidance R.6.5.1.2 specifies that for a well-defined endpoint:

- the training set must be obtained from experimental data generated with homogeneous experimental protocols, and

- the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement, which in this case includes OECD TG 421/422.

You specify that the effect that is modelled is: (i-ii)developmental toxicity, (iii-iv) estrogen receptor related effects, (v) androgen receptor related effects, and (vi) receptor related effects.

It is not clear and it cannot be excluded that the endpoint predicted by the (Q)SAR is not the same as the endpoint measured by the relevant test protocols and the training set data is not from homogeneous test protocols.

More specifically,

- There is lack of specific information on the endpoints.
- There are no experimental data, or when there are experimental data it is aggregated and sources of original (raw) data are not available.
- Species and test protocols are not specified.
- Details on test results are missing.
- The model is based on qualitative data and thus does not serve the purpose of filling data gap for an information requirement.

Therefore the endpoint of the model is not well defined and you have not established that the use of this model is a scientifically valid approach to meet this information requirement.

Conclusion

Thus, ECHA cannot verify and/or confirm that the cumulative conditions of Annex XI, Section 1.3 listed above are met. Therefore, you have not demonstrated the reliability of the provided information and this information is rejected.

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

1. 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.).

You have adapted this information requirement by using a WoE adaptation in accordance with Annex XI, section 1.2.
You have provided the following information:

i. OECD TG 202 study with the analogue substance tartaric acid (EC 201-766-0).
ii. Study similar to OECD TG 202 with the analogue substance tartaric acid (EC 201-766-0).
iii. Prediction of effect concentration to daphnids by VegaNIC v.1.0.8.
iv. Prediction of effect concentration to daphnids by T.E.S.T. v.4.1.

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

As explained under Appendix on Reasons common to several requests, Section 1, 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 performed according to OECD TG 202 must be provided. OECD TG 202 requires the study to investigate the following key investigation:

- the concentration of the test material leading to the immobilisation of 50% of daphnids at the end of the test is estimated.

Coverage of key investigations

All provided sources of information may provide information on the immobilization of daphnids.

However, the reliability of these sources of information is significantly affected by the deficiencies identified under Appendix on Reasons common to several requests, Section 1.

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

Reliability of the experimental studies i. and ii. listed above

To fulfil the information requirement, normally a study according to OECD TG 202 must be provided. The specifications of this test include:

- the test duration is 48 hours or longer;
- the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
- the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1);

- the test design (*e.g.* static or semi-static test, number of replicates) and the test procedure (*e.g.* composition of the test medium, loading in number of *Daphnia* per test vessel) are reported.

Your registration dossier provides the following information for the experimental studies i. and ii:

- the test duration was 24 hours for the study i. and 32 hours for the study ii.;
- no information about analytical monitoring of exposure concentrations throughout the test duration for the study i. and no analytical monitoring of exposure concentrations was conducted in the study ii.;
- information on the test design and procedure is missing from the registration dossier for the study i.

Based on the above, the listed above specifications are not met for neither of the provided experimental studies. Thus, there are critical methodological deficiencies significantly affecting their reliability.

As a conclusion, sources of information as indicated above, provide information on the immobilization of daphnids, but the provided information is not reliable.

Based on the assessment above, 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 in an OECD TG 202 study. Therefore, your adaptation is rejected.

In your comments on the draft decision, you provided study report for the hydrolysis study and for the short-term toxicity testing with invertebrates study with analogue substance tartaric acid (EC 201-766-0) which was not provided in the registration dossier. However, information neither on the analytical method nor on the results of the analytical determination of exposure concentrations throughout the test duration is reported in the study report. This is necessary to confirm that the concentration of the Substance being tested has been satisfactorily maintained and the effect concentrations can be based on nominal concentrations. It should be noted that hydrolysis is not the only possible mechanism of the losses of substances from the test solutions as well as the concentration of a substance in the prepared initial solution might differ from the expected nominal concentration. As the analytical determination of exposure concentrations throughout the test duration was not performed in the study, there are critical methodological deficiencies resulting in the rejection of the study results.

As explained above under Appendix on Reasons common to several requests provided information (in the registration dossier and in your comments on the draft decision) based on application of QSAR is rejected.

Therefore, the information requirement is not fulfilled.

As explained in the Appendix on Reasons common to several requests, section 0 in your comments on the draft decision you propose grouping of the listed substances in the "Tartaric acid and its salts" category and applying a read-across approach in accordance with Annex XI, Section 1.5. You propose to report in the registration dossier results of the short-term toxicity study with aquatic invertebrates with calcium tartrate which is available in the registration dossier of calcium tartrate.

ECHA considers that the proposed read-across approach is plausible and could fulfil the information gap as long as you comply with the conditions specified in the Appendix on Reasons common to several requests, section 0 about reporting of reliable source study(-ies),

selection of the maximum test concentration and estimation of effect concentration(s) for the target substance(s).

As the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

2. 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 adapted this information requirement by using a WoE adaptation in accordance with Annex XI, section 1.2.

You have provided the following information:

i. Experimental study where "*tartaric acid solution was used as solvent and it was tested to assess its toxicity (negative control). A concentration of 0.06% tartaric acid was resulted in no or little growth inhibition among all the strains tested: the highest value for inhibition was 11.3% for I. galbana.”*.

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

As explained under Appendix on Reasons common to several requests, Section 1, 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.

You have provided information from the single source in the registration dossier. However, information from a single source alone is insufficient to support weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of these critical deficiencies, ECHA has nevertheless assessed the reliability and relevance of the source of information provided.

To fulfil the information requirement, normally a study performed according to OECD TG 201 must be provided. OECD TG 201 requires the study to investigate the following key investigation:

- the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test are estimated.

Coverage of key investigations

The provided source of information may provide information on the inhibition of growth of algae.

However, the reliability of this source of information is significantly affected by the following deficiencies:

Reliability of experimental study

To fulfil the information requirement, normally a study according to OECD TG 201 must be provided. The specifications of this test include:

- 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}.
- the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within 20 % of the nominal or measured initial concentration throughout the test;
- information on the test design (e.g., number of replicates etc.), test conditions (e.g., biomass density at the beginning of the test) and biological results are reported.

Your registration dossier indicates that no analytical monitoring of exposure concentrations throughout the test duration was conducted and does not provide information on the test design (e.g., number of replicates etc.), test conditions (e.g., biomass density at the beginning of the test) and biological results for the provided study.

Based on the above, the listed above specifications are not met for the provided experimental study. Thus, there are critical methodological deficiencies significantly affecting its reliability.

As a conclusion, source of information as indicated above, provide information on the inhibition of growth of algae, but the information provided is not reliable.

Based on the assessment above, it is not possible to conclude, based on the source of information alone, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 201 study. Therefore, your adaptation is rejected.

In your comments on the draft decision, you provided study report for the hydrolysis study and for the algae growth inhibition study with analogue substance tartaric acid (EC 201-766-0) which was not provided in the registration dossier. However, information neither on the analytical method nor on the results of the analytical determination of exposure concentrations throughout the test duration is reported in the study report. This is necessary to confirm that the concentration of the Substance being tested has been satisfactorily maintained and the effect concentrations can be based on nominal concentrations. As noted above, hydrolysis is not the only possible mechanism of the loss of substances from the test solutions as well as the concentration of a substance in the prepared initial solution might differ from the expected nominal concentration. Furthermore, data on the algal biomass determined daily for each treatment group and control are not reported and therefore, it is not possible to independently assess if validity criteria of OECD TG 201 are met. Thus, there are critical methodological deficiencies resulting in the rejection of the study results.

As explained above under Appendix on Reasons common to several requests provided information in your comments on the draft decision based on application of QSAR is rejected.

Therefore, the information requirement is not fulfilled.

As explained in the Appendix on Reasons common to several requests, section 0 in your comments on the draft decision you propose grouping of listed there substances in the "Tartaric acid and its salts" category and applying a read-across approach in accordance with Annex XI, Section 1.5. You propose to report in the registration dossier results of the Growth inhibition study in aquatic plants with calcium tartrate which is available in the registration dossier of calcium tartrate.

ECHA considers that the proposed read-across approach is plausible and could fulfil the information gap as long as you comply with the conditions specified in the Appendix on Reasons common to several requests, section 0 about reporting of reliable source study(-ies), selection of the maximum test concentration and estimation of effect concentration(s) for the target substance(s).

As the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

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

1. 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 (Section 8.7.1) to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support of your adaptation, you have provided the following study records in your dossier:

(i) Four teratology studies (similar to EPA OTS 798.4700, Reproduction and Fertility Effects) performed with an analogue substance (tartaric acid, EC no 201-766-0) in rats, rabbits, mice and hamsters at doses < 300 mg/kg bw/day (1973)

(ii) One 150-day study performed with an analogue substance (sodium tartrate) in rabbits (1963) at a concentration of 7.7% in diet.

In your comments on the initial draft decision you provided

(iii) complementary information on your adaptation according to Annex XI, Section 1.2 (Weight of evidence);

(iv) (quantitative) structure-activity relationships estimations (Annex XI, Section 1.3)

We have assessed this information and identified the following issues:

a) Weight of evidence

As explained under Appendix on Reasons 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.

Sexual function and fertility

Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

The sources of information (i) provide information on maintenance of pregnancy and litter sizes. However, they do not inform on mating, fertility, parturition, lactation, organ weights and histopathology of reproductive organs and tissues, or nursing performance.

The source of information (ii) provides information on organ weights and histopathology of testes.

The sources of information (i-ii) provide some relevant information on several aspects of the sexual function and fertility, but not on all aspects that have to be covered, as defined above.

The EFSA report, which you refer to in your comments (iii) and consider as a key source of information, describes the sources of information (i-ii). The additional repeated dose studies included in the EFSA report provide relevant information on organ weights and histopathology of reproductive organs in both sexes.

Furthermore, as explained in the Appendix on Reasons common to several requests (Section 1), an EFSA finding is limited to the evaluation of risk incurred by the dietary exposure to a substance and does mean that the evaluated substance has been subject to an overall analysis of the intrinsic properties of the substance as required by the testing annexes under the REACH Regulation.

The other arguments you raised in your comments (see the Appendix on Reasons common to several requests (Section 1)), do not provide relevant information on sexual function and fertility.

The reliability of the sources of information (i-ii) is significantly affected by the following deficiency:
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 this test guideline specify for example that the highest dose level should aim to induce toxic effects.

The highest dose level in the sources of information (i and ii) did not induce any toxicity and you have not shown that the aim was to induce toxicity. Neither did they reach the limit dose level of 1000 mg/kg bw/day. Therefore, the dose level selection was too low, and the studies do not fulfil the criterion set in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

In conclusion, there are no reliable sources of information for sexual function and fertility.

Toxicity to offspring

Information on pre- and perinatal developmental toxicity reflected by litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

The sources of information (i) provide information on pre-natal developmental toxicity (litter sizes, postimplantation loss) but not on peri- and postnatal toxicity up to postnatal day 13 (postnatal litter sizes, survival, stillborns, clinical signs and body weights of pups). The source of information (ii) and the EFSA report do not provide any information of toxicity to offspring.

Therefore, there is lack of significant amount of information on various aspects of toxicity to offspring similar to foreseen to be investigated in an EU B.63/OECD TG 421. Furthermore, as indicated above under sexual function and fertility, the sources (i) providing relevant information, are not reliable.

Systemic toxicity

Information on systemic toxicity include information on clinical signs with specific observations, survival, body weights, food consumption, haematology, clinical biochemistry,

organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

The sources of information (i and ii) and the repeated dose studies included in the EFSA report provide some information on systemic toxicity.

However, information on the following aspects are missing: haematology, clinical biochemistry, and maternal toxicity during lactational period. Furthermore, the arguments provided in your comments (*"ADME data show lower internal exposure to tartaric acid in humans compared to rats" and "tartrate is not metabolised to oxalate"*) do not bring proof on lack of systemic effects.

Therefore, there is lack of information on some aspects of systemic toxicity foreseen to be investigated in an EU B.63/OECD TG 421. Furthermore, as indicated above under sexual function and fertility, the sources (i and ii) providing relevant information, are not reliable.

Conclusion on weight of evidence

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 properties foreseen to be investigated in EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, your adaptation is rejected.

b) Predictions by application of (quantitative) structure-activity relationships

As explained above under Appendix on Reasons common to several requests, the information provided in your comments on the draft decision, based on application of QSAR, is rejected.

Conclusion

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

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[2] administration of the Substance.

2. 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 adapted this information requirement by using a WoE adaptation in accordance with Annex XI, section 1.2.

You have provided the following information:

i. Prediction of effect concentration to fish by VegaNIC v.1.0.8.

ii. Prediction of effect concentration to fish by T.E.S.T. v.4.1.

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

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

As explained under Appendix on Reasons common to several requests, Section 1, 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 performed according to OECD TG 203 must be provided. OECD TG 203 requires the study to investigate the following key investigation:

- the concentration of the test material leading to the mortality of 50% of the juvenile fish at the end of the test is estimated.

Coverage of key investigations

All provided sources of information may provide information on the mortality of fish.

However, the reliability of these sources of information is significantly affected by the deficiencies identified under Appendix on Reasons common to several requests, Section 1.

As a conclusion, sources of information as indicated above, provide information on the mortality of fish, but provided information is not reliable.

Based on the assessment above, 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 in an OECD TG 203 study. Therefore, your adaptation is rejected

As explained above under Appendix on Reasons common to several requests provided information in your comments on the draft decision based on application of QSAR is rejected.

In your comments on the draft decision, you provided study report for the hydrolysis study and for the short-term toxicity testing with fish study with analogue substance tartaric acid (EC 201-766-0) which was not provided in the registration dossier. Study report of the short-term toxicity testing with fish provides information on mortalities and sub-lethal effects, a number of test animals per test concentration/control and fish loading. However, information neither on the analytical method nor on the results of the analytical determination of exposure concentrations throughout the test duration is reported. This is necessary to confirm that the concentration of the Substance being tested has been satisfactorily maintained and the effect concentrations can be based on nominal concentrations. As noted above, hydrolysis is not the only possible mechanism of the loss of substances from the test solutions as well as the concentration of a substance in the prepared initial solution might differ from the expected nominal concentration. Furthermore, study report notes that '*tests were performed at test substance concentrations of 10 mg/l, 5 mg/l, 2.5 mg/l, 1 mg/l and 0.5 mg/l*", i.e. last specification of OECD TG 203 noted above is not fulfilled. Thus, there are critical methodological deficiencies resulting in the rejection of the study results.

Therefore, the information requirement is not fulfilled.

As explained in the Appendix on Reasons common to several requests, section 0 in your comments on the draft decision you propose grouping of listed there substances in the "Tartaric acid and its salts" category and applying a read-across approach in accordance with Annex XI, Section 1.5. You propose to perform long-term toxicity testing on fish with one of the category members and to report this information in the registration dossier. You intend to use results of the long-term toxicity testing on fish as justification for an adaptation of the

short-term toxicity testing on fish.

ECHA considers that the proposed read-across approach is plausible and could fulfil the information gap as long as you comply with the conditions specified in the Appendix on Reasons common to several requests, section 0 about reporting of reliable source study(-ies), selection of the maximum test concentration and estimation of effect concentration(s) for the target substance(s).

As the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

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[3].

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[4].

[3] https://echa.europa.eu/practical-guides
[4] 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 20 January 2020.

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

In your comments you asked ECHA to *"include in the final Decision a transitional period of 12 monthsin order to comprehensively update the dossiers, thus formally including in the dossiers data offered with these comments for satisfying ECHA requests with existing data"*.

The time necessary to perform the required tests and update the CSA/CSR is considered in the deadline(s) set in the draft decision. It is your responsibility to submit or improve adaptations to the standard information requirements covered by the requests within the above deadline(s).

You may update your dossier at any point of time and submit compliant information to fulfil the information requirements covered by the requests. ECHA will only evaluate the updated dossier after the deadline of the final decision.

ECHA took into account your comments and did not amend the request(s) or the deadline.

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[5] 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)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

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[8]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

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

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.