~~Confidential~~

Helsinki, 24 June 2021

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

Date of submission of the dossier subject to this decision
26/03/2013

Registered substance subject to this decision ("the Substance")
Substance name: (+)-tartaric acid
EC number: 201-766-0
CAS number: 87-69-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed in A.1., A.2., A.3., B.2., C.2. and C.3. below by ***29 September 2022*** and all 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. Justification for an adaptation of short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.) based on the results of the Long-term toxicity testing on aquatic invertebrates requested below (Annex IX, Section 9.1.5.)

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

3. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: OECD TG 301A/B/C/D/E/F or OECD TG 310)

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

1. Justification for an adaptation of a Screening for reproductive/developmental toxicity based on the results of the Extended one-generation reproductive toxicity study requested below (Annex VIII, Section 8.7.1.)

2. Justification for an adaptation of short-term toxicity testing on fish (Annex VIII, Section 9.1.3.) based on the results of the Long-term toxicity testing on fish requested below (Annex IX, Section 9.1.6.)

C. Information required from all the Registrants subject to Annex IX of REACH

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

D. Information required from all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rat/rabbit)

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, specified as follows:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

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 X 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, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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

How to comply with your information requirements

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

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH

purposes". 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 and ready biodegradability 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. Furthermore, you propose to report in the registration dossier results of ready biodegradability studies with members of the category available in the registration dossiers of these members.

Moreover, in your comments on the draft decision you propose to perform long-term toxicity testing on aquatic invertebrates and 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 and ready biodegradability 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 and ready biodegradability 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 (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. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
3. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)
4. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
5. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

In your comments on the draft decision you have provided predictions by Organic Module Evaluation (ECHA understands by ECOSAR), Vega software for the above listed information requirements and predictions by Consensus method for the short-term toxicity testing on aquatic invertebrates and on fish. Furthermore, you have provided predictions for the ready biodegradability (Annex VII, Section 9.2.1.1.) by Vega software.

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

1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
3. Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)
4. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

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

(i) Information on aquatic toxicity and ready biodegradability 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 ECOSAR v1.00 for the aquatic toxicity endpoints listed above as supporting studies in the registration dossier in order to comply with the REACH information requirements.

Lack of documentation of the model (QMRF) and of the prediction (QPRF)

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.

Furthermore, 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 not provided information about the ECOSAR v1.00 model and predictions for any of information requirements listed above. In particular, you have not included QMRFs and a QPRFs in your registration dossier. Furthermore, you have not included QMRFs and a 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 these information requirements.

(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 and for the ready biodegradability (and persistence).

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 and ready biodegradability (and persistence) 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;

7) "*no similar compounds*" in the training set have been found;

8) "*accuracy of prediction for similar molecules found in the training set is not optimal*";

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 Chronic Toxicity by IRFMN 1.0.0: issues 6 and 7 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.;
- Aquatic invertebrates (*Daphnia magna*) Chronic Toxicity by IRFMN 1.0.0: issues 1 and 4;
- 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;
- Ready biodegradability by IRFMN 1.0.9: issues 1, 2, 4 and 8;
- Persistence (sediment) by IRFMN 1.0.0: issues 1, 2, 6 and 8;
- Persistence (sediment and soil) quantitative by IRFMN 1.0.0: issues 6 and 7;
- Persistence (soil) by IRFMN 1.0.0: issues 1 and 6;

- Persistence (water) by IRFMN 1.0.0: issue 1;

- Persistence (water) quantitative by IRFMN 1.0.0: issues 2, 6 and 7.

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 414 and 443.

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 endpoints predicted by the (Q)SAR are not the same as the endpoints 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 these information requirements.

Conclusion

Consequently, ECHA cannot verify that the cumulative conditions of Annex XI, Section 1.3 listed above are met. Therefore, the provided information based on application of QSAR is rejected.

2. Assessment of the Annex XI adaptation in your comments on the initial draft decision

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".*

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

- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.)

ECHA also understands that the above-listed pieces of information have also been submitted as additional information for the weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2 for the endpoint Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.).

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.

Besides the above common issues, 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.

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

1. Justification for an adaptation of short-term toxicity testing on aquatic invertebrates based on the results of the Long-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. OECD TG 202 key study conducted with tartaric acid (Cas No 87-69-4; EC No 201-766-0).
ii. Supporting experimental study with no standard guideline followed and conducted with tartaric acid (Cas No 87-69-4; EC No 201-766-0).
iii. Supporting information, prediction of short-term toxicity to daphnids by ECOSAR v1.00.
iv. Supporting information, prediction of short-term toxicity to mysid shrimp by ECOSAR v1.00.

We have assessed this information and identified the following issues:

Reliability of experimental studies

To fulfil the information requirement, a study must comply with OECD TG 202 (Article 13(3) of REACH). Therefore, the following specifications must be met:

- the test duration is 48 hours or longer;
- 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);
- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations are provided;
- the number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation.
-

Your registration dossier provides information showing the following:

- on study i. above:
    - information neither on the analytical method nor on the results of the analytical determination of exposure concentrations throughout the test duration are reported;
    - tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported;
- on study ii. above:
    - the test duration was 32 hours;

- no analytical monitoring of exposure was conducted;
- tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported.

Based on the above:

- the reporting of the study i. is not sufficient to conduct an independent assessment of its reliability; and

- there are critical methodological deficiencies resulting in the rejection of the study ii. results.

In your comments on the draft decision, you provided a study report for the hydrolysis study and for the key short-term toxicity testing with invertebrates study. Study report of the short-term toxicity testing with invertebrates provides information on the number of immobilised daphnids at the end of the test. 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. 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 key sudy, there are critical methodological deficiencies resulting in the rejection of the study i. results.

Therefore, the requirements of OECD TG 202 are not met for neither of the provided experimental studies.

Predictions by application of (quantitative) structure-activity relationships

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.

On this basis, the information requirement is not fulfilled.

The present decision requests the registrant(s) concerned to conduct and submit a long-term toxicity study on aquatic invertebrates (OECD TG 211; see Appendix C.2 for details). According to Annex VII, Section 9.1.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study on aquatic invertebrates does not need to be provided.

Because you still must comply with the information requirement in Annex VII, Section 9.1.1., you are requested to submit a justification for the adaptation provided in Annex VII, Section 9.1.1., Column 2, second indent.

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 provided the following information:

i. OECD TG 201 key study conducted with tartaric acid (Cas No 87-69-4; EC No 201-766-0).
ii. Supporting information, prediction of effect concentration (EC 50) to green algae by ECOSAR v1.00.
iii. Supporting information, prediction of chronic effect concentration (ChV) to green algae by ECOSAR v1.00.

We have assessed this information and identified the following issues:

Reliability of experimental studies

To fulfil the information requirement, a study must comply with OECD TG 201 (Article 13(3) of REACH). Therefore, the following specifications must be met:

- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;
- the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;
- number of replicates per test concentration/control and biomass density at the beginning of the test are reported.

Your registration dossier provides an OECD TG 201 study i. showing the following:

- information neither on the analytical method nor on the results of the analytical determination of exposure concentrations throughout the test duration are reported;
- tabulated data on the algal biomass determined daily for each treatment group and control are not reported;
- number of replicates per test concentration/control and biomass density at the beginning of the test are not reported.

In your comments on the draft decision, you provided study report for the hydrolysis study and for the key algae growth inhibition study. Study report of the algae growth inhibition study provides information on the number of replicates per test concentration/control and biomass density at the beginning of the test. 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, 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.

Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. Therefore, the requirements of OECD TG 201 are not met for the study i.

Predictions by application of (quantitative) structure-activity relationships

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.

On this basis, 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 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.

3. Ready biodegradability

Ready biodegradability is an information requirement in Annex VII to REACH (Section 9.2.1.1.).

You have provided:

i. OECD TG 306 key study conducted with tartaric acid (Cas No 87-69-4; EC No 201-766-0).
ii. Supporting study, American Public Health Association (1989) Standard Methods for the examination of Water and Waste water, 17th ed., Washington DC, Biochemical Oxygen Demand test conducted with tartaric acid (Cas No 87-69-4; EC No 201-766-0).

We have assessed this information and identified the following issues:

To fulfil the information requirement, a study must comply with the OECD TG 301 or 310 (Article 13(3) of REACH). OECD test guideline 306 explicitly indicates that results of those tests (shake flask and closed bottle) "*are not to be taken as indications of ready biodegradability, but are to be used specifically for obtaining information about the biodegradability of chemicals in marine environments*" (Guidnace R.7b). Furthermore, use of the non-standard data (e.g. biochemical studies using mixed or pure culture) in the assessment of the degradation potential of the substance should be fully documented and justified by the registrant (Guidance R.7b).

In the registration dossier, including the Chemical Safety Report, you conclude that the Substance is readily biodegradable. This conclusion is based on the key and supporting studies reported in the dossier. However, it is not justified how the conclusion that the Substance is readily biodegradable was reached on the basis of the provided studies, none of which is standard ready biodegradability study.

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.

On this basis, the information requirement is not fulfilled.

As explained in the Appendix on Reasons common to several requests, section 0 in your comments on the initial draft decision you propose grouping 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 ready biodegradability studies with the members of the category available in the registration dossiers of these members.

ECHA considers that the proposed read-across approach is plausible and could fulfil the information gap as long as the reliable study(-ies) with the member(s) of the category will be reported in the registration dossier.

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. Justification for an adaptation of a Screening for reproductive/developmental toxicity based on the results of the Extended one-generation reproductive toxicity study

Screening for reproductive/developmental toxicity is a standard information requirement under Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

You have included an adaptation according to Annex VIII, Section 8.7.1., Column 2. You provided four pre-natal developmental toxicity studies in your dossier. However, as explained in Appendix C.1., the studies provided for the pre-natal developmental toxicity information requirement are not accepted. Therefore, your adaptation is rejected.

The present decision requests the registrants concerned to generate and submit an extended one-generation reproductive toxicity study (EOGRTS) (see Appendix D.2). Once an EOGRTS is available, according to Column 2 of Annex VIII, Section 8.7.1. and in order to prevent unnecessary animal testing, a screening for reproductive/developmental toxicity does not therefore need to be conducted. While you still have to comply with the information requirement in Annex VIII, Section 8.7.1., you are requested to submit a justification for the adaptation based on Column 2 of that provision.

2. Justification for an adaptation of short-term toxicity testing on fish based on the results of the Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Annex VIII, Section 9.1.3, Column 2 or a general adaptation rule under Annex XI.

You have provided the following information:

i. OECD TG 203 key study with the tartaric acid (Cas No 87-69-4; EC No 201-766-0).
ii. Supporting information, prediction of short-term toxicity to freshwater fish by ECOSAR v1.00.
iii. Supporting information, prediction of short-term toxicity to saltwater fish by ECOSAR v1.00.

We have assessed this information and identified the following issues:

Reliability of experimental studies

To fulfil the information requirement, a study must comply with OECD TG 203 (Article 13(3) of REACH). Therefore, the following specifications must be met:

- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations are provided;
- mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) are reported. The frequency of observations includes at least 2 observations within the first 24 hours and at least two observations per day from day 2 to 4;
- number of test animals per test concentration/control and fish loading are reported;

- test should be be performed for 96 hours at the concentrations of the test material enabling estimation of the mortality of 50% of the juvenile fish at the end of the test (i.e. 96 hours LC50) or the highest test concentration should be, at least, as high as the lowest concentration of following: 100 mg/L or at the limit of solubility in the test medium under test conditions, or at the threshold concentration as defined in Annex 1 of OECD TG 203 in order to demonstrate that the LC50 is greater than this concentration.

Your registration dossier provides an OECD TG 203 showing the following:
- information neither on the analytical method nor on the results of the analytical determination of exposure concentrations throughout the test duration are reported;
- tabulated data on mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) obtained on at least 2 observations within the first 24 hours and at least two observations per day from day 2 to 4 for each treatment group and control are not reported;
- number of test animals per test concentration/control and fish loading are not reported.

Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability.

Furthermore, 96 hours LC50 is reported as above 100 mg/l, water solubility of the substance is above 100 mg/l and the lowest EC50-value for algae or Daphnia reported in the dossier (as discussed under respective sections above, algae and short-term Daphnia toxicity data reported in the dossier are not compliant) is 51.4 mg/l. However, the nominal test concentrations did not enable estimation of definite LC50 and the highest test concentration was below 51.4 mg/l. Thus, last specification of OECD TG 203 noted above is not fulfilled.

In your comments on the draft decision, you provided study report for the hydrolysis study and for the key short-term toxicity testing with fish study. 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 requirements of OECD TG 203 are not met.

Predictions by application of (quantitative) structure-activity relationships

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.

On this basis, the information requirement is not fulfilled.

The present decision requests the registrant(s) concerned to conduct and submit a long-term toxicity study on fish (OECD TG 210; see Appendix C.3 for details). According Annex VIII, Section 9.1.3., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study on fish does not need to be provided.

Because you still must comply with the information requirement in Annex VIII, Section 9.1.3., you are requested to submit a justification for the adaptation provided in Annex VIII, Section 9.1.3., Column 2, second indent.

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: Reasons to request information required under Annex IX of REACH

1. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH, Section 8.7.2.

Information provided in your dossier

You have provided (i) four teratology studies (similar to OECD TG 414) performed with the Substance in rats, rabbits, mice and hamsters at doses < 300 mg/kg bw/day (1973).

Although you do not explicitly claim an adaptation, ECHA understands that the information provided was submitted in order to meet the required information by way of adaptation under Annex XI, Section 1.1.2.

Annex XI, Section 1.1.2 enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods where a number of cumulative conditions are met, in particular:

1. Highest dose level should aim to induce some toxicity.
2. Adequacy for the purpose of classification and labelling and/or risk assessment.

We have assessed this information and identified the following issues:

1. The highest dose levels in the studies you have submitted did not induce any developmental and/or maternal 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 OECD TG 414.

2. Based on the above, the provided information cannot be considered to be adequate for classification and labelling and/or risk assessment.

Information provided in your comments on the initial draft decision

In your comments on the initial draft decision you provided

(i) an adaptation according to Annex XI, Section 1.2 (Weight of evidence); see Appendix on Reasons common to several requests (Section 2.)

(ii) (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 in the 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 8.7.2 at Annex IX includes similar information that is produced by the OECD TG 414 on one species. The following aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

Pre-natal developmental toxicity

Pre-natal developmental toxicity includes information after pre-natal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

The sources of information (i) included in your dossier provide relevant information on embryonic/foetal survival, growth and structural malformations and variations.

The EFSA report, which you refer to in your comments and consider as a key source of information, describes the sources of information (i) but does not provide further relevant information on embryonic/foetal survival, growth or structural malformations and variations.

The other arguments you raised in your comments (see the Appendix on Reasons common to several requests (Section 2.)), do not provide relevant information on embryonic/foetal survival, growth and structural malformations and variations.

The reliability of the 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 pre-natal developmental toxicity, the study has to meet the requirements of OECD TG 414. The criteria of this test guideline specify for example that the highest dose level should aim to induce some developmental and/or maternal toxicity.

As already explained above, the highest dose level in the sources of information included in your dossier, did not induce any developmental and/or maternal 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 OECD TG 414.

Taken together, the relevant information on prenatal developmental toxicity provided is not reliable.

Maternal toxicity

Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

The sources of information (i) provide information on maternal toxicity. However, as indicated under pre-natal developmental toxicity above, the information is not reliable.

The EFSA report and the additional arguments in your comments do not provide further relevant information on maternal toxicity.

Maintenance of pregnancy

Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

The sources of information (i) provide information on maintenance of pregnancy. However, as indicated under pre-natal developmental toxicity above, the information is not reliable.

The EFSA report and the additional arguments in your comments do not provide further relevant information on maintenance of pregnancy.

Taken together, the sources of information provide some relevant information on prenatal developmental toxicity, maternal toxicity, and maintenance of pregnancy. However, the provided sources of information are not reliable based on reasons indicated above.

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 OECD TG 414. 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

Your adaptations are rejected and the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[2] administration of the Substance.

In your comments on the initial draft decision you noted that on the first page of this decision it was indicated that the study should be performed with inhalation administration. That clerical error has been corrected. The study must be performed with oral administration of the Substance.

In your comments on the initial draft decision you propose that, if your weight of evidence adaptation is not accepted by ECHA, the studies requested in this decision are performed using the Substance or one of the members of the Category "Tartaric acid and its salts" [i.e. 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 "*request ECHA to formally accept at Decision stage [..] that the studies will be performed with one substance representative of the Category (source substance) and used for all the members of the Category (target substances)*".

ECHA considers the proposed read-across approach plausible and could fulfil the information gaps. However, it is in your discretion to generate and provide the necessary supporting information in order to justify your proposed read-across adaptation to fulfil the information requirement in accordance with the requirements of Section 1.5 of Annex XI to REACH.

2. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have provided the following information:

i. a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:

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

"Long -term aquatic toxicity testing is not proposed *by the registrant as the chemical assessment does not indicate a need to investigate further effects on aquatic organisms. This is based on the knowledge that the substance has low aquatic toxicity, is readily biodegradable and has a low bioaccumulation potential*".

ii. Supporting information, prediction of long-term toxicity to daphnids by ECOSAR v1.00.

iii. Supporting information, prediction of long-term toxicity to mysid shrimp by ECOSAR v1.00.

We have assessed this information and identified the following issues:

Adaptation according to Annex IX, Section 9.1., Column 2

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

Predictions by application of (quantitative) structure-activity relationships

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.

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 aquatic invertebrates with one of the category members and to report this information in the registration dossier.

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.

On this basis, the information requirement is not fulfilled.

3. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have provided the following information:

i. a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification: "*Long -term aquatic toxicity testing is not proposed by the registrant as the chemical assessment does not indicate a need to investigate further effects on aquatic*

organisms. This is based on the knowledge that the substance has low aquatic toxicity, is readily biodegradable and has a low bioaccumulation potential".

ii. Supporting information, prediction of 14 day toxicity to fish by ECOSAR v1.00.
iii. Supporting information, prediction of long-term toxicity to freshwater fish by ECOSAR v1.00.
iv. Supporting information, prediction of long-term toxicity to saltwater fish by ECOSAR v1.00.

We have assessed this information and identified the following issues:

Adaptation according to Annex IX, Section 9.1., Column 2

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

Predictions by application of (quantitative) structure-activity relationships

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.

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.

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.

On this basis, the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

Appendix D: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

Information provided in your dossier

You have provided four teratology studies (similar to OECD TG 414) performed with the Substance in rats, rabbits, mice and hamsters at doses < 300 mg/kg bw/day (1973).

Although you do not explicitly claim an adaptation, ECHA understands that the information provided was submitted in order to meet the required information by way of adaptation under Annex XI, Section 1.1.2.

Annex XI, Section 1.1.2 enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods where a number of cumulative conditions are met, in particular:

1. Highest dose level should aim to induce some toxicity.
2. Adequacy for the purpose of classification and labelling and/or risk assessment.

We have assessed this information and identified the following issues:

1. The highest dose levels in the studies you have submitted did not induce any developmental and/or maternal toxicity and you have not shown that the aim was to induce toxicity. Neither did they reach the limit dose of 1000 mg/kg bw/day. Therefore, the dose level selection was too low, and the studies do not fulfil the criterion set in OECD TG 414.

2. Based on the above, the provided information cannot be considered to be adequate for classification and labelling and/or risk assessment.

Information provided in your comments on the initial draft decision

In your comments on the initial draft decision you provided

(iii) an adaptation according to Annex XI, Section 1.2 (Weight of evidence); see Appendix on Reasons common to several requests (Section 2.)

(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 Section C.1, the sources of information provide some relevant information on prenatal developmental toxicity, maternal toxicity, and maintenance of pregnancy. However, the provided sources of information are not reliable based on reasons indicated under Section C.1.

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

Your adaptations are rejected and the information requirement is not fulfilled.

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study (request C.1. in this decision).

The study must be performed with oral[3] administration of the Substance.

In your comments on the initial draft decision you propose that, if your weight of evidence adaptation is not accepted by ECHA, the studies requested in this decision are performed using the Substance or one of the members of the Category "Tartaric acid and its salts" [i.e. 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 "*request ECHA to formally accept at Decision stage [..] that the studies will be performed with one substance representative of the Category (source substance) and used for all the members of the Category (target substances)*".

ECHA considers the proposed read-across approach plausible and could fulfil the information gaps. However, it is in your discretion to generate and provide the necessary supporting information in order to justify your proposed read-across adaptation to fulfil the information requirement in accordance with the requirements of Section 1.5 of Annex XI to REACH.

2. Extended one-generation reproductive toxicity study

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X (Section 8.7.3.) to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

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

In support of your adaptation, you have provided the following sources of information and arguments without documentation:

Information provided in your dossier

Sources of information:

(i) Acute oral and dermal studies with LD50-values > 2000 mg/kg (robust study summary included in the dossier).

(ii) A two-year dietary feeding study with NOAELs > 2460 mg/kg bw/day (robust study summary included in the dossier).

(iii) Teratology studies in four species with oral administration of the Substances at doses ≤274 mg/kg bw/day during organogenesis showing no maternal or developmental effects (robust study summaries included in the dossier).

(iv) Data on absorption and excretion (robust study summaries included in the dossier and in addition you refer to a published scientific article with open access (The Journal of Biological Chemistry, 1933, 100: 349-355).

Arguments without documentation:

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

(v) No indications of reproductive toxicity have been reported in relation to tartaric acid occurring naturally in fruits and wine, or its use as a food additive and laxative. You did not provide data to support your justification.
(vi) No significant maternal or developmental toxicity has been observed in rats exposed to succinate tartrate at 1g/kg/day (robust study summary not provided; you refer to a published scientific article without open access, Food and Chemical Toxicology, April 1989, 27(4): 249-253).
(vii) No fertility effects have been reported for metoprolol tartrate up to 500 mg/kg (robust study summary not provided; you refer to brief pharmaceutical summary documents).

Information provided in your comments on the initial draft decision

In your comments on the initial draft decision you provided
(viii) an adaptation according to Annex XI, Section 1.2 (Weight of evidence); see Appendix on Reasons common to several requests (Section 2.)
(ix) (quantitative) structure-activity relationships estimations (Annex XI, Section 1.3)

We have assessed this information and identified the following issues:

a) Weight of evidence

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

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

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

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

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

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex X includes similar information that is produced by the OECD TG 443 design as specified in this decision. At general level, it includes information on 1) sexual function and fertility, 2) toxicity to offspring, 3) systemic toxicity, - and 4) if column 2 triggers are met, also information on sexual function and fertility of the

offspring, toxicity to F2 offspring, developmental neurotoxicity and/or developmental immunotoxicity.

As no supportive documentation is provided for arguments (v, vi and vii) they cannot be assessed and your claims (v, vi, vii) regarding sexual function and fertility, toxicity to offspring, and systemic toxicity cannot be verified.

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, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

Source (ii) should provide relevant information on organ weights and histopathology of reproductive organs in both sexes (however, not absolutely clear from the documentation).

Source (iii) provides relevant information on maintenance of pregnancy.

Sources (i and iv) do not provide any information on sexual function and fertility, source (i) refers to acute toxicity studies with no investigations on sexual function and fertility, and source (iv) refers to toxicokinetic properties, not to sexual function and fertility.

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

The other arguments you raised in your comments (see the Appendix on Reasons common to several requests (Section 2)), do not provide relevant information on sexual function and fertility.

Therefore, the only relevant information is on limited aspects of sexual function and fertility: organ weights and histopathology of reproductive organs (ii and EFSA report) and maintenance of pregnancy (iii).

However, as explained in the Appendix on Reasons common to several requests (Section 2), 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. Furthermore, the sources of information (iii) have a deficiency that reduces the reliability. As already indicated in Appendix C and D, Section 1, the dose levels of these studies do not follow the criteria set out in OECD TG 414 for a pre-natal developmental toxicity study. Because of that it is not possible to conclude if the Substance has or has not an effect on the maintenance of pregnancy.

Taken together, there is no information on functional fertility (mating, fertility, gestation (length), parturition and lactation, and no reliable information on maintenance of pregnancy.

Due to lack of significant amount of relevant and reliable information on sexual function and fertility, it is not possible to conclude on that property.

Toxicity to the offspring

Toxicity to offspring must cover information on deaths before, during or after birth, growth, external malformations, clinical signs, sexual maturity, oestrous cyclicity, organ weights and histopathology of reproductive organs in adulthood and other potential aspects of toxicity to offspring.

Source (iii) provides relevant information on toxicity to the offspring before birth.

Sources (i, ii and iv) and the EFSA report do not provide any information on toxicity to offspring; sources (i and ii) refer to acute and repeated toxicity studies with no investigations on matings and offspring, and source (iv) refers to toxicokinetic properties, not to toxicity to offspring.

Therefore, the only relevant source of information (iii) contains information on a limited aspect of toxicity to offspring: toxicity before birth (deaths and growth before birth, and malformations) but not on toxicity after birth up to adulthood as foreseen to be investigated in an OECD TG 443 (deaths, growth, clinical signs, sexual maturity, oestrous cyclicity, organ weights and hispathology of reproductive organs in adulthood).

However, the source of information (iii) has a deficiency that reduces its reliability as indicated above under sexual function and fertility as well as in Appendix C and D, section 1: the dose levels of these studies do not follow the criteria set out in OECD TG 414 for a prenatal developmental toxicity study. Because of that it is not possible to conclude if the Substance has or has not an effect on toxicity to offspring (before birth).

Taken together, there is no information on toxicity to offspring after birth (deaths, growth, clinical signs, sexual maturity, oestrous cyclicity, organ weights and hispathology of reproductive organs in adulthood) and no reliable information on toxicity to offspring before birth (deaths, growth, malformations).

Due to lack of relevant and reliable information on toxicity to offspring, it is not possible to conclude on that property.

Systemic toxicity

Systemic toxicity must include information on clinical signs, survival, body weights, food consumption, haematology (full-scale), clinical chemistry (full-scale), organ weights and histopathology of non-reproductive organs (full-scale) and other potential aspects of systemic toxicity in the parental P and F1 generation up to adulthood.

The sources of information (i and iii) provide relevant information on clinical signs, survival and body weights. Information is limited to very short time period (i) and during pregnancy only (iii).

The two-year chronic study (ii) and the repeated dose studies included in the EFSA report provide relevant information on several aspects of systemic toxicity in P generation, including clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs. However, there is no information on systemic toxicity in F1 generation up to adulthood.

ECHA notes that although systemic toxicity was not reported based on the source of information (ii) or in the EFSA report (for the P generation), the data (iv) included in the toxicokinetics section of your dossier show that systemic absorption can occur (14% estimated absorption of the oral dose in humans) and systemic toxicity is therefore possible. The data in the old reference used in your Weight of Evidence justification (The Journal of

Biological Chemistry, 1933, 100: 349-355) indicates that approximately 17% of orally ingested tartaric acid was excreted in urine of humans. Systemic uptake/distribution of the substance was not investigated. 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.

The source of information (i) has a deficiency that reduces its reliability: the information is after a single dose only, not informing on effects after repeated dosing.

The source of information (iii) has a deficiency that reduces its reliability as indicated above under sexual function and fertility as well as in Appendix C and D, section 1: the dose levels of these studies do not follow the criteria set out in OECD TG 414 for a prenatal developmental toxicity study. Because of that it is not possible to conclude if the Substance has or has not an effect on the systemic toxicity (during pregnancy).

Therefore, the only relevant and reliable information for systemic toxicity (for P generation) is the source of information (ii) and data in the EFSA report. However, as indicated above there is no information at all on systemic toxicity of the F1 generation.

Due to lack of all of the relevant and reliable information on systemic toxicity in F1 generation, it is not possible to conclude on that property.

Conclusion on weight of evidence

Taken together, the sources of information as indicated above provide relevant and reliable information on

- sexual function and fertility: weight and histopathology of reproductive organs (in P generation), but lacking information on functional fertility (mating, fertility, gestation (length), parturition and lactation, and not reliable information on maintenance of pregnancy
- systemic toxicity, but is limited for one generation and lacking for the F1 generation up to adulthood.

Furthermore, there is no information on toxicity to offspring after birth and no reliable information on toxicity to offspring before birth.

Therefore, a significant amount of essential investigations are limited or totally lacking that would inform on sexual function and fertility, toxicity to offspring and systemic toxicity in order to conclude on these aspects, and totally on properties of reproductive toxicity.

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 an OECD TG 443 study.

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.

<u>Conclusion</u>

Based on the above, your adaptation is rejected and the information you provided does not fulfil the information requirement.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[4]

Therefore, the requested premating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and must be included.

Species and route selection

The study must be performed in rats with oral[5] administration of the Substance.

In your comments on the initial draft decision you propose that, if your weight of evidence adaptation is not accepted by ECHA, the studies requested in this decision are performed using the Substance or one of the members of the Category "Tartaric acid and its salts" [i.e. 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 "*request ECHA to formally accept at Decision stage [..] that the studies will be performed with one substance representative of the Category (source substance) and used for all the members of the Category (target substances)*".

ECHA considers the proposed read-across approach plausible and could fulfil the information gaps. However, it is in your discretion to generate and provide the necessary supporting information in order to justify your proposed read-across adaptation to fulfil the information requirement in accordance with the requirements of Section 1.5 of Annex XI to REACH.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort

[4] ECHA Guidance R.7a, Section R.7.6.
[5] ECHA Guidance R.7a, Section R.7.6.2.3.2.

3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[6].

[6] ECHA Guidance R.7a, Section R.7.6.

Appendix E: 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[7].

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[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

Appendix F: 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.

However, there was a clerical error at the first page of the initial draft decision, requesting a PNDT study by inhalation instead of oral administration, which has now been corrected.

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 G: List of references - ECHA Guidance[9] 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)[10]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[11]

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[12]

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