~~Confidential~~

Helsinki, 24 June 2021

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

Date of submission of the dossier subject to this decision
25/09/2019

Registered substance subject to this decision ("the Substance")
Substance name: Potassium sodium tartrate
EC number: 206-156-8
CAS number: 304-59-6

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., 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)

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 a Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.) based on the results of the Long-term toxicity testing on fish request 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 Annexes VII and VIII to REACH, for registration at 10-100 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

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

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

- 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.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

In your comments on the initial draft decision you have submitted a new proposal for read-across approach in accordance with Annex XI, Section 1.5 for the following endpoints:

- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Finally, in your general comment on the draft decision you note that "*we suggest to perform the requested tests in a single substance and read-across the related ones in order to reduce animal testing as much as possible, since dossiers of tartaric acid and its salts (NaK, HK, KK and Ca) have been assessed and the animal tests requested are very similar (reproduc-tive toxicity and ecotoxicology).*"

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Predictions for (eco)toxicological properties').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

A. Predictions for (eco)toxicological properties

You read-across between the following substances:

- Disodium succinate hexahydrate (EC 612-073-1)
- Fumaric acid (EC 203-743-0)

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

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

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

- Malic acid (EC 230-022-8)
- Disodium succinate (EC 205-778-7)

as source substances and the Substance as target substance.

Based on your comments on the initial draft decision, for the endpoints Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.), Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.), Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.) you read-across between the following substance:

- a complexation product of sodium tartrate with iron trichloride

as source substance and the Substance as target substance.

Based on your comments on the initial draft decision, for the endpoint Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) you read-across between the following substance:

- a complexation/reaction product of sodium tartrate [D(−)-and L(+)-tartaric acid and mesotartaric acid], sodium hydroxide, and iron trichloride (FemTA)

as source substance and the Substance as target substance.

You have reasoned the prediction on the basis of structural similarity of the source and target substances.

Absence of well-founded hypothesis

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled to apply grouping and read-across. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).

A read-across hypothesis needs to establish why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the substances[5]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. Your read-across hypothesis is that the structural similarity between the source substances and your Substance is a sufficient basis for predicting the properties of your Substance.

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

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

Aquatic toxicity source studies not meeting Annex XI requirements

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read-across should:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

Among others there are following source studies that you have used in your read-across approach:

1) short-term fish toxicity study with fumaric acid;
2) short-term aquatic invertebrates toxicity study with malic acid;
3) algal growth inhibition study with fumaric acid.

These studies correspond respectively to OECD TGs 203, 202 and 201.

According to the provisions of Annexes VII-VIII, Section 9.1, information on short-term aquatic invertebrates toxicity, growth inhibition study aquatic plants and short-term fish toxicity as specified in the OECD TGs 202, 201 and 203, respectively shall be provided. The following specifications must be met for the studies performed according to these OECD TGs:

- exposure concentrations of the test material is confirmed by the analytical monitoring throughout the test duration;
- information on the test design (e.g. number of replicates etc.) and test conditions (e.g. test temperature etc.) is reported;
- short-term fish toxicity test duration is 96 hours or longer.

Your registration dossier provides aquatic toxicity studies with source substances showing the following:

- no analytical monitoring of exposure was conducted in neither of the three studies;
- information on the test design and test conditions is not reported for the studies 1 and 3;
- duration of the study 1 was 48 hours.

Thus, at least some of the specifications listed above are not met for each of three aquatic toxicity studies performed with source substances. Consequently, study 1 listed above does not cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3). Furthermore, all three studies listed above are not reliable. Therefore, they are not adequate for the purpose of classification and labelling and/or risk assessment, and cannot be used as source studies in the grouping and read-across approach.

Read-across approach to complexation products submitted in your comments on the draft decision

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

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

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

As your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s), information characterising the rate and extent of the hydrolysis of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common (hydrolysis) product and to assess the impact of the exposure to the parent compounds.

You have not provided any experimental data or other adequate and reliable information, about the hydrolysis/formation of common product by the the Substance and the source substance. In the absence of this information, you have not provided supporting evidence establishing that the proposed common product is formed as assumed in your read-across hypothesis.

Furthermore, exposure to the Substance and the source substance(s) may also lead to exposure to other compounds than the common compound of interest. The impact of exposure to these non-common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

You have not provided information characterising the exposure to the non-common compounds resulting from exposure to the Substance and of the source substance(s). No experimental data or other adequate and reliable information addressing the impact of exposure to these non-common compounds is included in the documentation of your read-across approach. In the absence of such information, you have not established that a reliable prediction of the property under consideration of the Substance can be derived on the basis of your read-across hypothesis. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Moreover, according to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

The reporting of the source studies with complexation products you proposed in your comments on the draft decision to be used in the read-across approach is not sufficient to conduct an independent assessment of their reliability. Therefore, it cannot be concluded if the conditions listed above are met for the studies with the source substance.

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

C. Alternative read-across proposed in the comments on the draft decision

In your general comment on the draft decision you note that "*we suggest to perform the requested tests in a single substance and read-across the related ones in order to reduce*

animal testing as much as possible, since dossiers of tartaric acid and its salts (NaK, HK, KK and Ca) have been assessed and the animal tests requested are very similar (reproduc-tive toxicity and ecotoxicology).”

ECHA understands that you propose grouping the following substances “*tartaric acid and its salts (NaK, HK, KK and Ca)”, 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), in the category and applying a read-across approach in accordance with Annex XI, Section 1.5 for the reproductive and aquatic toxicity tests requested. You propose to perform requested tests with one of the category members and to report this information in the registration dossier.

ECHA considers that the proposed grouping of *“tartaric acid and its salts (NaK, HK, KK and Ca)”* in the category with suggestion *“to perform the requested tests in a single substance”* and applying a read-across approach to other category members is plausible and could fulfil the information gaps. However, it is in your discretion to generate and provide reliable studies with a source substance which would be adequate for the purpose of classification and labelling and/or risk assessment as well as generate and provide the necessary supporting information in order to justify your proposed read-across adaptation to fulfil the information requirements in accordance with the requirements of Section 1.5 of Annex XI to REACH.

Furthermore, it should be noted that the molecular weight of the counter-ion (non-common transformation product) of the source substance(s) should be considered:

- for the selection of the maximum test concentration/dose, in order to ensure that the test concentration/dose of the common tartaric acid anion relevant (i.e. expected to be present when maximum concentration/dose 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 effect concentration/level for the target substance(s).

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

You have adapted the following 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.)
- 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.)

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 have nevertheless assessed the validity of your adaptation.

The two issues identified below are relevant for all the environmental information requirements in which you invoked a weight of evidence.

Grouping and read-across rejected

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

QSAR predictions rejected

Section 3 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.

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

3. 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:

In your dossier:

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.)

In your comments on the initial draft decision:

1. Pre-natal developmental toxicity (Annex IX, Section 8.7.2)
2. Extended one-generation toxicity (Annex X, Section 8.7.3)

Furthermore, in your comments on the draft decision you have provided predictions by Organic Module Evaluation (ECOSAR) for the long- and short-term aquatic toxicity endpoints.

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.

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

a) Evaluation of predictions on aquatic toxicity endpoints in your dossier and in comments on the draft decision

You have provided QSAR predictions by Danish National Food Institute (MultiCASE platform) for the aquatic toxicity endpoints listed above in order to comply with the REACH information requirements in the registration dossier and in your comment on the draft decision predictions for the long- and short-term aquatic toxicity endpoints by Organic Module Evaluation.

Inadequate documentation of the model (QMRF)

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 model applied, i.e. QSAR Model Reporting Format (QMRF). For the algorithm definition you note in this document that "*details available on request*".

Thus, the information in the QMRF is not sufficient to conclude on the unambiguous algorithm. In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

Lack of documentation of the prediction (QPRF)

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

Furthermore, you have not included QMRFs and a QPRFs for the long- and short-term aquatic toxicity predictions by Organic Module Evaluation provided in your comments on the draft decision.

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

b) Evaluation of predictions on reproductive and developmental toxicity endpoints in your comments on the initial draft decision

You have provided information based on several QSAR models / tools.

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 TG 443.

Predictions by CAESAR Developmental Toxicity Model.

You specify that the effect that is modelled is developmental toxicity.

You have provided a (Q)SAR model which is based on data generated using the following methodology: FDA protocol. Chemical compounds have been chosen by a combination of data according to the TERIS and the FDA guidelines. Both sources are on evaluation of the existing human and animal data on potentially teratogenic chemicals, which are used by physicians for reference. The TERIS compilation is skewed toward a complete evaluation of the animal data; whereas the FDA discussions emphasize human studies or case reports, with some reference to pertinent animal studies. Reference to exact protocol is not provided in QMRF.

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 protocol and the training set data is not from homogeneous test protocols.
More specifically,

- There is lack of specific information on the endpoint.
- There are no experimental data found in the CAESAR model training set for the target compound.
- 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 requirement.

Predictions by Danish battery approach

You specify that the effect that is modelled is developmental toxicity.

You have provided QSAR predictions by Danish National Food Institute (MultiCASE platform) for developmental toxicity which is based on data generated using a training set commercially available from MultiCASE Inc. The training set for this is composed of data from the Teratogen Information System (TERIS) and a compilation in which the United States Food and Drug Administration (FDA) definitions were used to quantify potential for developmental toxicity from drugs used during pregnancy. The training set consists of clinical, epidemiologic and animal data.

It is not clear and it cannot be excluded that the endpoints predicted by the (Q)SAR are not the same as the endpoint measured by the relevant test protocol.

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.

Lack of or inadequate documentation of the prediction (QPRF)

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

Predictions by Danish battery approach

Reference to the exact protocol was not provided. The information you provided about the prediction has the following deficiencies:

(i) Inadequate documentation of the relationship between the modelled substance and the defined applicability domain.

(ii) Inadequate documentation of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

In absence of such information, ECHA cannot establish that the prediction can be used to meet these information requirements.

The prediction is not adequate due to low reliability

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).

Predictions by DART schema for developmental toxicity

Your registration dossier provides some predictions by DART schema. You did not provide any reference to the exact protocol.

The DART schema for developmental toxicity is published in the scientific literature. In the OECD QSAR Toolbox, DART schema is an adaptation of the framework for identifying chemicals with structural features, associated with the potential to act as reproductive or developmental toxicants, implemented as profiler (OECD QSAR Toolbox disclaimer: The structural boundaries used to define the chemical classes or alerting groups responsible for the binding with biological macromolecules, represent structural functionalities in the molecule which could be used for building chemical categories for subsequent data gap filling. They are not recommended to be used directly for prediction purposes as SARs).

The prediction(s) for the Substance used as input are not reliable because modelling of DART in QSAR approach does not follow the original idea of DART expert sytem. The results are qualitative (positive/negative), or not known (most often). Predictions for the substance are negative but these are not found suitable to fill a data gap due to lack of documentation. It is also not clear if the results are obtained with the OECD QSAR Toolbox, or with Danish implementation of the DART schema.

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

c) Conclusion

You have provided in the dossier document describing the model applied, i.e. QSAR Model Reporting Format (QMRF). However, you have not provided sufficient documentation for the QSAR predictions provided in the registration dossier for any of the endpoints listed above. In particular, you have not included QSAR Prediction Reporting Format (QPRF) in your technical dossier and the information in the QMRF is not sufficient to conclude on the unambiguous algorithm.

Furthermore, for the long- and short-term aquatic toxicity predictions by Organic Module Evaluation provided in your comments on the draft decision ECHA cannot establish that the predictions can be used to meet respective information requirements.

Finally, you have not established that the approaches applied for predictions on reproductive and developmental toxicity endpoints in your comments on the initial draft decision are scientifically valid to meet the information requirements.

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

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.).

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:

- OECD TG 202 study with source substance disodium succinate hexahydrate.
- OECD TG 202 with source substance malic acid**.**
- Prediction of effect concentration to daphnids by MultiCASE.

As explained under Appendix on Reasons common to several requests, Section 2, 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 investigations:

- 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 2.

As a conclusion, sources of information as indicated above, provide information on the immobilization of daphnids, 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 202 study. Therefore, your adaptation is rejected.

Information in your comments on the draft decision:

In your comments on the draft decision, you provided the following information:
- QSAR prediction by Organic Module Evaluation (ECOSAR).

Your comments on the draft decision are addressed in the Appendix on Reasons common to several requests and as concluded there ECHA cannot establish that the prediction can be

used to meet this information requirement and information based on application of QSAR is rejected.

Thus, the data gap remains and 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 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.

2. Growth inhibition study aquatic plants

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

ECHA understands that 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 201 study with source substance disodium succinate hexahydrate (flagged by you as key study).
ii. No guideline followed study with "*The standard solutions used were* [redacted]*.*" (flagged by you as supporting study).
iii. UBA Algal growth inhibition test (proposed 1984) with source substance fumaric acid (flagged by you as supporting study).
iv. Prediction of effect concentration to algae by MultiCASE (flagged by you as weight of evidence).

As explained under Appendix on Reasons common to several requests, Section 2, 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 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

All provided sources of information may provide information on the inhibition of growth of algae.

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

In addition the relevance and reliability of these sources of information is significantly affected by the following deficiency:

Reliability of experimental study ii. listed above

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, sources of information as indicated above, provide information on the inhibition of growth of algae, 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 201 study. Therefore, your adaptation is rejected.

Information in your comments on the draft decision:

In your comments on the draft decision, you provided the following information:
- proposal for read-across approach to a complexation product of sodium tartrate with iron trichloride as source substance in accordance with Annex XI, Section 1.5.;
- proposal for grouping "*tartaric acid and its salts (NaK, HK, KK and Ca)"* in the category and applying a read-across approach in accordance with Annex XI, Section 1.5.;
- QSAR prediction by Organic Module Evaluation (ECOSAR).

Your comments on the draft decision are addressed in the Appendix on Reasons common to several requests.

ECHA cannot establish that the prediction by Organic Module Evaluation can be used to meet this information requirement and information based on application of QSAR is rejected. Your proposed read-across approach to a complexation product of sodium tartrate with iron trichloride does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and therefore, is rejected.

ECHA considers that the proposed grouping of *"tartaric acid and its salts (NaK, HK, KK and Ca)"* in the category with suggestion "*to perform the requested tests in a single substance"* and applying a read-across approach to other category members 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 1.C. about generation and reporting of reliable source study(-ies) in the registration dossier, selection of the maximum test concentration and estimation of effect concentration(s) for the target substance(s).

Thus, the data gap remains and the information requirement is not fulfilled.

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 adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

You included a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (2003) with an analogue substance (Disodium succinate hexahydrate (EC 612-073-1) in your dossier.

As explained in Appendix Reasons common to several requests, the read across is rejected and the study provided for the screening for reproductive/developmental toxicity information requirement is 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 request 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 a Short-term toxicity testing on fish based on the results of the Long-term toxicity testing on fish

As explained under Appendix on Reasons common to several requests, Section 2, 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 2.

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.

Information in your comments on the draft decision:

In your comments on the draft decision, you provided the following information:

- QSAR prediction by Organic Module Evaluation (ECOSAR).

Your comments on the draft decision are addressed in the Appendix on Reasons common to several requests and as concluded there ECHA cannot establish that the prediction can be used to meet this information requirement and information based on application of QSAR is rejected.

Thus, the data gap remains and the information requirement is not fulfilled.

The present decision requests the registrants 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.

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 (Section 8.7.2.) to REACH.

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Annex XI, Section 1.2 of REACH (weight of evidence).

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

Information in your dossier:

(i) Four teratology studies (similar to OECD TG 414) 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)

Information in your comments on the initial draft decision:

In your comments on the initial draft decision, you provided the following information. However, you indicated that the comments were related to Annex IX, 8.7.2. -Pre-natal developmental toxicity study in a second species. As this decision does not contain any request for a PNDT in a second species at Annex IX, we have addressed the provided information and your comments here.

(ii) Repeated dose / reproductive study (reported to be in compliance with OECD TG 421, 422, 408) performed with an analogue substance ([redacted]) in rats (2013);
(iii) EFSA Panel on Food Additives and Flavourings evaluation of L(+)-tartaric acid, sodium tartrates, potassium tartrates, potassium sodium tartrate and calcium tartrate as food additives (2020);
(iv) QSAR approach.

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 8.7.2 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) provide relevant information on embryonic/foetal survival, growth and structural malformations and variations.

The source of information (ii) provides relevant information on embryonic/foetal survival and growth but it does not provide information on structural malformations and variations as described in OECD TG 414. Therefore, it only provides limited information on this key element in general.

The source of information (iii) does not provide relevant information on embryonic/foetal survival, growth or structural malformations and variations.

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

To be considered compliant and to generate information concerning the effects of the Substance on 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.

The highest dose level in the sources of information (i) 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.

As explained under Appendix on Reasons common to several requests, your adaptation under Annex XI, Section 1.5 for the source substance which is used in the source of information (ii) is rejected.

As explained under Appendix on Reasons common to several requests, your adaptation under Annex XI, Section 1.3, related to the source of information (iv) is rejected.

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-ii) provide information on maternal toxicity.

However, as indicated under pre-natal developmental toxicity above, the sources of information (i-ii) do not provide reliable information.

The sources of information (iii-iv) do not provide 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-ii) provide information on maintenance of pregnancy.

However, as indicated under prenatal developmental toxicity above, the sources of

information (i-ii) do not provide reliable information.

The sources of information (iii-iv) do not provide 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 (i-ii) 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.

Conclusion

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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[7] administration of the Substance.

In your comments on the initial draft decision you propose that, if your adaptations are not accepted by ECHA, "*suggest to perform the requested tests in a single substance and read-across the related ones in order to reduce animal testing as much as possible, since dossiers of tartaric acid and its salts (NaK, HK, KK and Ca* [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)]*) have been assessed and the animal tests requested are very similar*".

ECHA considers that the proposed read-across approach is 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 adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.
You have provided OECD TG 211 key study with the source substance disodium succinate.

As explained in the Appendix on Reasons common to several requests, section 1, your grouping and read-across approach is rejected. Therefore, your adaptation is rejected.

Information in your comments on the draft decision:

In your comments on the draft decision, you provided the following information:
- proposal for read-across approach to a complexation product of sodium tartrate with iron trichloride as source substance in accordance with Annex XI, Section 1.5.;
- proposal for grouping following substances "*tartaric acid and its salts (NaK, HK, KK*

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

and Ca)" in the category and applying a read-across approach in accordance with Annex XI, Section 1.5.;
- QSAR prediction by Organic Module Evaluation (ECOSAR).

Your comments on the draft decision are addressed in the Appendix on Reasons common to several requests.

ECHA cannot establish that the prediction by Organic Module Evaluation can be used to meet this information requirement and information based on application of QSAR is rejected. Your proposed read-across approach to a complexation product of sodium tartrate with iron trichloride does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and therefore, is rejected.

ECHA considers that the proposed grouping of *"tartaric acid and its salts (NaK, HK, KK and Ca)"* in the category with suggestion *"to perform the requested tests in a single substance"* and applying a read-across approach to other category members 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 1.C. about generation and reporting of reliable source study(-ies) in the registration dossier, selection of the maximum test concentration and estimation of effect concentration(s) for the target substance(s).

Thus, the data gap remains and 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: "In Annex IX of Regulation (EC) No 1907/2006, it is laid *down that long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. This is not considered to be the case. The low estiimated Kow of the substance, its very low acute toxicity (well in excess of 100 mg/L) and its rapid biodegradability do not justify further studies. Tartrates, as well as salts of other dibasic carboxyllic acids are organic acids part of common metaboplic routes of multiple organisms and are readily taken up and degraded. See further discussion in toxicokinetics section.*".

We have assessed this information and identified the following issue:

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.

Information in your comments on the draft decision:

In your comments on the draft decision, you provided the following information:
- proposal for read-across approach to a complexation product of sodium tartrate with iron trichloride as source substance in accordance with Annex XI, Section 1.5.;
- proposal for grouping following substances *"tartaric acid and its salts (NaK, HK, KK*

and Ca)" in the category and applying a read-across approach in accordance with Annex XI, Section 1.5.;
- QSAR prediction by Organic Module Evaluation (ECOSAR).

Your comments on the draft decision are addressed in the Appendix on Reasons common to several requests.

ECHA cannot establish that the prediction by Organic Module Evaluation can be used to meet this information requirement and information based on application of QSAR is rejected. Your proposed read-across approach to a complexation product of sodium tartrate with iron trichloride does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and therefore, is rejected.

ECHA considers that the proposed grouping of *"tartaric acid and its salts (NaK, HK, KK and Ca)"* in the category with suggestion *"to perform the requested tests in a single substance"* and applying a read-across approach to other category members 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 1.C. about generation and reporting of reliable source study(-ies) in the registration dossier, selection of the maximum test concentration and estimation of effect concentration(s) for the target substance(s).

On this basis, the data gap remains and 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.

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Annex XI, Section 1.2 of REACH (weight of evidence).

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

Information provided in your dossier

(i) Four teratology studies (similar to OECD TG 414) 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)

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

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.

Information provided in your comments on the initial draft decision

(i) You provided comments on Annex IX, 8.7.2, Pre-natal developmental toxicity study in a second species. As this decision does not contain any request for a PNDT in a second species at Annex IX, we have addressed your comments in section C.1. (PNDT in a first species at Annex IX). ECHA's assessment of the information provided in your comment applies for Annex X, 8.7.2. (PNDT in a second species) as well. Moreover, we notice that in your comments, you have not provided any additional info on pre-natal developmental toxicity in a second species under Annex X.

(ii) (Quantitative) structure-activity relationships estimations (Annex XI, Section 1.3). 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.

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

Information on study design

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 shall be performed with oral[8] administration of the Substance.

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

In your comments on the initial draft decision you propose that, if your adaptations are not accepted by ECHA, "*suggest to perform the requested tests in a single substance and read-across the related ones in order to reduce animal testing as much as possible, since dossiers of tartaric acid and its salts (NaK, HK, KK and Ca* [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)]*) have been assessed and the animal tests requested are very similar*".

ECHA considers that the proposed read-across approach is 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 to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

In your dossier, you have provided a justification for data waiving: *"the study does not need to be conducted because (i) the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), (ii) it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and (iii) there is no or no significant human exposure*."

In your comments on the initial draft decision you included further arguments:

(i) "*Extended one-generation reproductive toxicity study: Given the ionic nature of potassium sodium tartrate, its very high water solubility in excess of 100 mg/L and low Kow it is not expected that it will be significantly absorbed through the stratum corneum of the skin. Absorption is also predicted to be limited through biological membranes such as those in intestinal villus and in the lung alveoli, although as demonstrated by oral studies some 17 -20% of tartaric acid / tartrates administered orally is absorbed*".

(ii) "*The amounts absorbed are rapidly distributed, partially metabolised and excreted unchanged in urine or as oxidised metabolites (CO2). Animal and human studies performed upon laboratory animals and in humans indicate that tartaric acid and tartrates administered orally are to a large scale (80%) metabolised by bacteria in the intestines and excreted. Approximately 20% is absorbed and partially excreted via urine, exhaled air and faeces and part is metabolised in tissues, especially by the blood, liver, kidneys and bones. Maximum serum levels of tartrate are detected 1 h after intramuscular or oral dosing, witha subsequent biphasic decline with half-lifes of 3 and 53 h respectively. Labelled material can be detected in bone even 192 h after the last dose*".

(iii) "*Labelling experiments reveal that metabolised tartrate is oxidised and excreted as CO2. Toxicokinetic information indicates rapid metabolism and elimination of tartaric acid and of its salts and available information corresponding to an oral chronic toxicity test performed in rat with monosodium tartrate do not indicate any abnormalities in testes or ovaries after a 2 year study*".

(iv) "*In addition, its low toxicity and absence of indication of reproductive effects after a long history of dietary exposure of humans to tartrates demonstrate the*

absence of reproductive toxicity, hence perform animal tests would be unnecessary".

(v) New QSAR approaches were submitted.

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

Information included in your dossier

According to Annex X, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, two of them being:

- that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
- that there is no or no significant human exposure.

You justified the adaptation by stating that the Substance is of low toxicological activity, there is no systemic toxicity/absorption and no significant human exposure. However, you have not substantiated your claim on no systemic toxicity. Although there is no evidence of toxicity in the available studies, you have not provided any toxicokinetic data to support your claim on no systemic absorption. Thus, lack of systemic absorption has not been proven. Furthermore, the uses included in the dossier indicate that humans are exposed.

Information included in your comments on the initial draft decision

It is understood that in your comments (i-iv) you mainly provided further arguments to strengthen your adaptation according to Annex X, Section 8.7., Column 2.

You explained that approximately 20% of the Substance is absorbed after oral administration and that it has a half-life of approximately 53 hours after oral administration. The oral route is considered a relevant route of exposure. Thus the information you provided does not fulfil the Annex X, Section 8.7., Column 2 criterion "no systemic absorption occurs via relevant routes of exposure". Although reproductive effects have not been observed upon dietary human exposure (via food) that can not be considered as proof of no reproductive toxicity of the Substance under REACH. Please note that a finding that there is no such risk does not mean that the evaluated substance does not present any (other) concern to human health or to the environment or presuppose an overall analysis of the intrinsic properties of the substance. Under Article 41, ECHA needs to verify that the information provided is in compliance with the respective testing Annexes under REACH and if a data gap is identified, ECHA has to request the test.

Further, in relation to your comment (v) ECHA understands that you wish to adapt this information requirement according to Annex XI, Section 1.3. As explained in the Appendix on Reasons common to several requests, your QSAR adaptation is rejected.

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

<u>The specifications for the study design</u>

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.[91]

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[10] administration of the Substance.

In your comments on the initial draft decision you propose that, if your adaptations are not accepted by ECHA, "*suggest to perform the requested tests in a single substance and read-across the related ones in order to reduce animal testing as much as possible, since dossiers of tartaric acid and its salts (NaK, HK, KK and Ca* [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)]*) have been assessed and the animal tests requested are very similar*".

ECHA considers that the proposed read-across approach is 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 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[11].

[9] ECHA Guidance R.7a, Section R.7.6.
[10] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[11] 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[12].

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[13].

[12] https://echa.europa.eu/practical-guides
[13] 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.

ECHA took into account your comments and did not amend the requests.

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[14] 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)[15]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[15]

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[16]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[14] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[15] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[16] 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 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]

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.