

Helsinki, 24 June 2021

**Addressees**

Registrant(s) of JS\_PotassiumHydrogenTartrate as listed in the last Appendix of this decision

**Date of submission of the dossier subject to this decision**

31/05/2018

**Registered substance subject to this decision ("the Substance")**

Substance name: Potassium hydrogen tartrate

EC number: 212-769-1

CAS number: 868-14-4

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

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

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

1. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)
2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

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

1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats
2. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

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

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to VIII of REACH", respectively.

**Information required depends on your tonnage band**

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

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

### **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<sup>1</sup> under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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<sup>1</sup> 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. Assessment of your read-across approach under Annex XI, Section 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:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

Furthermore, in your general comment on the draft decision for the above mentioned endpoints as well as for the short-term toxicity testing on fish (Annex VIII, Section 9.1.3) 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<sup>2</sup> and related documents<sup>3, 4</sup>.

### A. Predictions for (eco)toxicological properties based on read-across approach to complexation products

Based on your comments on the initial draft decision, for the endpoints Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.) and Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.) you read-across between the following substances:

- a complexation product of sodium tartrate with iron trichloride

as source substance and the Substance as target substance.

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<sup>2</sup> 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](https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9)

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

<sup>4</sup> 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>

Based on your comments on the initial draft decision, for the endpoint Screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1.) you read-across between the following substances:

- 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<sup>5</sup>. 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.

#### *Read-across approach to complexation products*

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*"<sup>6</sup>. 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.

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<sup>5</sup> Guidance on information requirements and chemical safety assessment, Chapter [R.6: QSARs and grouping of chemicals](#).

<sup>6</sup> 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 (reproductive 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).

### **1. 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:

- 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 deficiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence 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 issues identified below is relevant for all the environmental information requirements in which you invoked a weight of evidence.

#### Grouping and read-across rejected

Section 0 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 2 of the present Appendix identifies deficiencies of the information based on application of (quantitative) structure-activity relationships (QSAR) submitted under your weight of evidence adaptations.

Your weight of evidence approach has 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.

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

You have provided information based on application of (quantitative) structure-activity relationships (QSAR) 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. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

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.

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

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 endpoint 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 endpoint predicted by the (Q)SAR are not the same as the endpoint 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 this 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 endpoint predicted by the (Q)SAR is 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 this information requirement.

*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 this information requirement.

*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 system. 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 endpoint in your comments on the initial draft decision are scientifically valid to meet the information requirement.

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. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

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

You have provided the following information:

- i. OECD TG 202 study with the analogue substance tartaric acid (EC 201-766-0).
- ii. Prediction of effect concentration to daphnids by MultiCASE.

As explained under Appendix on Reasons common to several requests, Section 1, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

To fulfil the information requirement, normally a study performed according to OECD TG 202 must be provided. OECD TG 202 requires the study to investigate the following key parameter:

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

#### Coverage of key investigations

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

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

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

#### Reliability of the experimental study

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

- the test duration is 48 hours or longer;
- the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
- the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1);
- the test design (e.g. static or semi-static test, number of replicates) and the test procedure (e.g. composition of the test medium, loading in number of *Daphnia* per test vessel) are reported.

Your registration dossier provides following information for the experimental study:

- the test duration was 24 hours;
- no information about analytical monitoring of exposure concentrations throughout the test duration;
- information on the test design and procedure is missing from the registration dossier.

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 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:

- 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).

We have assessed this information and identified the following issues:

*a. Data in your comments on the initial draft decision*

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 0.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 that basis, the data gap remains and the information requirement is not fulfilled.

There is a parallel dossier evaluation process to request the joint submission registrants concerned to generate and submit a long-term toxicity study on aquatic invertebrates. Unnecessary animal testing must be avoided. Therefore, to fulfil the information requirement covered by this endpoint, a justification for an adaptation based on column 2 of the present information requirement should be considered instead of the standard test.

## 2. Growth inhibition study aquatic plants

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

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

You have provided the following information:

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

As explained in the Appendix on Reasons common to several requests, Section 1, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

- 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 1.

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

### Reliability of experimental study

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

- the concentrations of the test material are measured at least at the beginning and end of the test:
  - 1) at the highest, and

- 2) at the lowest test concentration, and
  - 3) at a concentration around the expected EC<sub>50</sub>.
- 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 0.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. Screening for reproductive/developmental toxicity**

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.

*Information in your dossier:*

We understand that you have provided an adaptation according to Annex IX, Section 8.7., Column 2, by stating that the study does not need to be conducted because the substance is of low toxicological activity, no systemic absorption occurs via relevant routes of exposure, and there is no or no significant human exposure. However, Screening for reproductive/developmental toxicity is an information requirement under Annex VIII to REACH and we have to assess it accordingly under this Annex.

*Information in your comments on the initial draft decision:*

- (i) Repeated dose / reproductive study (reported to be in compliance with OECD TG 421, 422, 408) performed with an analogue substance (██████) in rats (2013);
- (ii) 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);
- (iii) QSAR approach.

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).

We have assessed the information and identified the following issues:

*Assessment of the Column 2 adaptation under Annex VIII, Section 8.7.*

According to Annex VIII, Section 8.7.1, Column 2, first paragraph, third intent, the corresponding study does not need to be conducted if relevant human exposure can be excluded in accordance with Annex XI section 3.

In your dossier you provided only the identified uses: manufacture, formulation and repacking and uses at industrial sites. You have included several PROCs for the identified uses e.g. PROC 3, 4, 8a, 9. No other information has been given for the uses and related exposure to workers.

ECHA notes that as no details on exposure scenarios, conditions of use and/or exposure estimates are included in the dossier or CSR, the information provided cannot be considered as proof of excluding relevant human exposure.

ECHA notes that in order to justify the omission of the standard information requirement, the human exposure assessment should be in accordance with Annex XI section 3. According to Annex XI sections 3.1 and 3.2 testing may be omitted based on the exposure scenarios developed in the Chemical Safety Report and in all cases adequate justification and documentation shall be provided based on a thorough and rigorous exposure assessment in accordance with section 5 of Annex I. All this information is missing from your dossier.

Based on the above, your adaptation is rejected.

*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 8.7.1 at Annex VIII includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

*Sexual function and fertility*

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

The source of information (i) provides relevant information on sexual function and fertility.

The EFSA report, which you refer to in your comments (ii) describes teratogenicity studies which provide some information on information on sexual function and fertility. The additional repeated dose studies included in the EFSA report provide relevant information on organ weights and histopathology of reproductive organs in both sexes.

*Toxicity to offspring*

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

The source of information (i) provides relevant information on toxicity to offspring. The EFSA report (ii) provides limited information of toxicity to offspring.

*Systemic toxicity*

Information on systemic toxicity include information on clinical signs with specific observations, survival, body weights, food consumption, haematology, clinical biochemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

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

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

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 (i) 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 (iii) is rejected.

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

Furthermore, an EFSA finding is limited to the evaluation of risk incurred by the dietary exposure to a substance and does not 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.

Taken together, the sources of information provide some relevant information on reproductive/developmental toxicity. 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.

#### Conclusion

The information you provided does not fulfil the information requirement.

#### Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral<sup>7</sup> 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.

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<sup>7</sup> ECHA Guidance R.7a, Section R.7.6.2.3.2.

## 2. Short-term toxicity testing on fish

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

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

You have provided the following information:

- i. Prediction of effect concentration to fish by MultiCASE.

As explained in the Appendix on Reasons common to several requests, Section 1, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

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

To fulfil the information requirement, normally a study performed according to OECD TG 203 must be provided. OECD TG 203 requires the study to investigate the following key parameter:

- 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

The provided source of information may provide information on the mortality of fish.

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

As a conclusion, source 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 the source of information alone, 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:

- 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);
- ECHA understands that since "*there is a parallel dossier evaluation process to request*

*the joint submission registrants concerned to generate and submit a long-term toxicity study on fish”, you intend to share generated data on long-term toxicity on fish with other registrants of the joint submission and will submit “an adaptation based on column 2 of the present information requirement in order to avoid unnecessary animal testing”.*

Your comments on the draft decision in respect of proposed grouping and provided QSAR predictions 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.

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 0.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.

There is a parallel dossier evaluation process to request the joint submission registrants concerned to generate and submit a long-term toxicity study on fish. Unnecessary animal testing must be avoided. Therefore, to fulfil the information requirement covered by this endpoint, a justification for an adaptation based on column 2 of the present information requirement should be considered instead of the standard test. ECHA acknowledges that you intend to share generated data on long-term toxicity on fish with other registrants of the joint submission and will submit a justification for an adaptation based on column 2 of the present information requirement.

## **Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes**

### **A. Test methods, GLP requirements and reporting**

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries<sup>8</sup>.

### **B. Test material**

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 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.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers<sup>9</sup>.

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<sup>8</sup> <https://echa.europa.eu/practical-guides>

<sup>9</sup> <https://echa.europa.eu/manuals>

## **Appendix D: Procedure**

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 10 March 2020.

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

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

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.



**Appendix E: List of references - ECHA Guidance<sup>10</sup> 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)<sup>11</sup>

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)<sup>12</sup>

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<sup>13</sup>

<sup>10</sup> <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

<sup>11</sup> <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

<sup>12</sup> <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

<sup>13</sup> <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

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

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

**Appendix F: Addressees of this decision and the corresponding information requirements applicable to them**

You must provide the information requested in this decision for all REACH Annexes applicable to you.

<b>Registrant Name</b>	<b>Registration number</b>	<b>Highest REACH Annex applicable to you</b>
██████████	██████████████████	██████████

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.