~~Confidential~~

Helsinki, 24 June 2021

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

Date of submission of the dossier subject to this decision
12/10/2017

Registered substance subject to this decision ("the Substance")
Substance name: Calcium tartrate
EC number: 221-621-5
CAS number: 3164-34-9

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed in A.2, B.2. and B.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 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

B. 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)

C. 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 VIII 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

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

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

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

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

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

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

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

Information in your dossier

- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.)
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Annex XI adaptation in your comments on the initial draft decision

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

- "*Therefore, the Addressees invoke EFSA risk assessment as adaptation under Annex XI to claim that further toxicological testing for reproductive and developmental effects*

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

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

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

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.

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

Besides the above common issues, your weight of evidence approach has deficiencies that that are specific for these information requirements individually. The specific deficiencies are set out under the information requirement concerned in the Appendices below.

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

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

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

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

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

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

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

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

Information generated by application of various QSARs applied by you raises the same deficiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when several cumulative conditions are met, in particular:

1. the substance falls within the applicability domain of the QSAR model;
2. the results are adequate for classification and labelling and/or risk assessment.

You have provided QSAR predictions for the analogue substance tartaric acid (EC No 201-766-0) by ECOSAR v1.11 for the aquatic toxicity endpoints listed above in your registration dossier in order to comply with the REACH information requirements.

You have provided in the dossier documentation supporting applied model.

We have assessed this information and identified the following issues:

> Based on the information provided in the registration dossier, i.e. the Substance is organic salt soluble in water as well as you noted in the IUCLID dossier, Section 4.21 "*the dissociation constant study does not need to be performed in accordance with section 1 of REACH Annex XI, since salts are reaction products of acids and bases that retain their ionic character*", the Substance is considered to be present in the ionised form(s) (i.e. is ionisable) at environmentally relevant pHs (4-9).
>
> For the prediction of aquatic toxicity for the tartaric acid you applied ECOSAR v.1.11 model for 'neutral organics' class. Furthermore, it is noted in the prediction documentation that the predicted aquatic toxicity values ((no-)effect concentrations) were compensated by an application of generic factor of 10 due to the presence of "*acid moiety found*" in the structure of the substance.
>
> Acids, such as tartaric acid, are not included in the definition of applied ECOSAR v.1.11 model for 'neutral organics' class and there is no justification provided by you why application of the generic factor of 10 would compensate for that. Furthermore, the 'neutral organic' class definition is not suitable for predicting aquatic toxicity of substances that are ionisable.
>
> Thus, you have not demonstrated that the Substance was falling within the applicability domain of the ECOSAR v.1.11 nor that the provided predictions are adequate for classification and labelling and/or risk assessment.

Lack of documentation of the model and of the prediction

Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

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

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

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

You have not included QMRFs and a QPRFs for the aquatic toxicity predictions by Organic Module Evaluation and Consensus method provided in your comments on the draft decision.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- MOA toxicity classification by EPA T.E.S.T. 1.0.0: issues 1 and 2;
- Verhaar classification by TOXTREE 1.0.0: issue 3;
- Fish acute classification by SarPy/IRFMN 1.0.2: issue 1;
- Fish Acute Toxicity by KNN/Read-Across 1.0.0: issues 4 and 5;
- Fish Acute Toxicity by NIC 1.0.0: issues 1, 2 and 4;
- Fish Acute Toxicity by IRFMN 1.0.0: issues 1, 2 and 6;

- Fish Acute Toxicity by IRFMN/Combase 1.0.0: issues 1, 4 and 5 etc.;

- Fish Chronic Toxicity by IRFMN 1.0.0: issues 6 and 7 etc.;

- Fish (Fathead Minnow) Acute Toxicity by EPA 1.0.7: issues 1 and 4;

- Fish (Fathead Minnow) Acute Toxicity by KNN/IRFMN 1.1.0: the Substance has both, (double) carboxyl acid and (double) alcohol functional groups with no other functional groups present in the molecule, while the training set contains acids (without alcohols), alcohol (without acids), ester, and alcohols with ester functional group; thus, ECHA considers that there is a lack of sufficiently similar substances in the training set;

- Aquatic invertebrates (*Daphnia magna*) Chronic Toxicity by IRFMN 1.0.0: issues 1 and 4.

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

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

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

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

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

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

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

Modelled endpoint not well defined

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

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

- the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement, which in this case includes OECD TG 414 and 443.

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

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

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

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

Conclusion

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

Appendix A: 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.

ECHA understands that you have adapted this information requirement according to according to Annex VIII, Section 8.7.1., Column 2.

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

(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).

In addition, you have provided one supporting repeated dose toxicity study:

(ii) One 150-day repeated dose toxicity study with an analogue substance (sodium hydrogen tartrate, EC no 208-400-9) in male rabbits

In your comments on the initial draft decision you provided

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

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

Column 2 adaptation

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in one species, e.g external, skeletal and visceral malformations and variations has to be investigated as described in OECD TG 414. However, as explained in B.1., the studies (i) provided for the pre-natal developmental toxicity information requirement are not accepted. Therefore, your adaptation is rejected.

Repeated dose toxicity study

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

- Dosing of the Substance for a minimum of four weeks for males and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation.
- Examination of parameters for sexual function and fertility such as those for mating and fertility/ duration of gestation, parturition, lactation and weight and histopathology of reproductive organs and tissues.
- Monitoring of oestrus cycles.
- Examination of offspring parameters such as /number and sex of pups/stillbirths and live births/ gross abnormalities/ pup body weight/ litter weight/anogenital distance/ number of nipples/areolae in male pups.

The study (ii) was performed with male animals only. It investigates general toxicity and provides information on histopathology of testes, but does not involve females or investigate effects on reproductive toxicity or development. Therefore, this study does not fulfil the information requirement.

Predictions by application of (quantitative) structure-activity relationships

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

Conclusion

The present decision requests the registrants concerned to generate and submit an extended one-generation reproductive toxicity study (EOGRTS) (see Section C.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 request below

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

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

i. Prediction of effect concentration to fish by VegaNIC v.1.0.8.
ii. Prediction of effect concentration to fish by T.E.S.T. v.4.1.

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

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

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

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

Coverage of key investigations

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

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

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

QSAR predictions rejected

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when several cumulative conditions are met, in particular:

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

You have provided QSAR predictions by VegaNIC v.1.0.8 and by T.E.S.T. v.4.1 for the short-term fish toxicity.

You have provided in the dossier documentation supporting applied models.

We have assessed this information and identified the following issues:

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

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

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

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

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

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

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

Inadequate documentation of the model (QMRF) for T.E.S.T. v.4.1

Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

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

You have provided in the dossier document describing the toxicity model for fish applied without a definition of the applicability domain.

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

Inadequate documentation of the prediction (QPRF) for T.E.S.T. v.4.1

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

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

You have provided in the dossier a QPRF document providing description of prediction of toxicity for fish without information about the relationship between the modelled substance and the defined applicability domain.

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

Thus, ECHA cannot verify and/or confirm that the cumulative conditions of Annex XI, Section 1.3 listed above are met for the provided QSAR predictions by VegaNIC v.1.0.8 and by T.E.S.T. v.4.1. Therefore, the reliability of the provided information based on application of QSARs is significantly affected.

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

Based on the assessment above, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 203 study. Therefore, your adaptation is rejected.

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

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

Therefore, the information requirement is not fulfilled.

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

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

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

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

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

Appendix B: 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 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).

(ii) One study in which an analogue substance (L-tartaric acid) was injected into the air cell or yolk of chicken eggs (1973), dose 8 mg/kg.

In your comments on the initial draft decision you provided

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

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

We have assessed this information and identified the following issues:

a) Weight of evidence

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

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 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 and ii) provide relevant information on embryonic/foetal survival, growth and structural malformations and variations.

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

The other arguments you raised in your comments (see the Appendix on Reasons common to several requests (Section 1.)), do not provide relevant information on embryonic/foetal survival, growth and 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 and ii) 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.

Regarding the source of information (ii), the chicken eggs study has not been accepted /validated as an international (OECD) test method to predict prenatal developmental toxicity for regulatory uses (hazard classification and risk assessment). Furthermore, it uses non-mammalian species without *in utero* development of embryos/foetuses, non-relevant route of administration (injection into the air cell or yolk), and unknown embryonic/foetal exposure period. Therefore, the limited information from the source (ii) is not reliable.

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

Maternal toxicity

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

The sources of information (i) provide information on maternal toxicity. The study design of (ii) does not include maternal exposure.

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

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

Maintenance of pregnancy

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

The sources of information (i) provide information on maintenance of pregnancy. The study design of (ii) does not include pregnancy.

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

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

Taken together, the sources of information (i-ii) provide 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.

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

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

Conclusion

Based on the above, the information you provided do 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[2] administration of the Substance.

In your comments on the initial draft decision you propose that, if your weight of evidence adaptation is not accepted by ECHA, the studies requested in this decision are performed using the Substance or one of the members of the Category "Tartaric acid and its salts" [i.e. tartaric acid (EC 201-766-0), sodium potassium tartrate (EC 206-156-8), potassium hydrogen tartrate (EC 212-769-1), dipotassium tartrate (EC 213-067-8), and calcium tartrate (EC 221-621-5)]. You "*request ECHA to formally accept at Decision stage [..] that the studies will be performed with one substance representative of the Category (source substance) and used for all the members of the Category (target substances)*".

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

2. Long-term toxicity testing on aquatic invertebrates

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

You have adapted this information requirement using QSAR predictions in accordance with Annex XI, section 1.3.

You have provided ECOSAR v1.11 prediction for this endpoint for the analogue substance tartaric acid (EC No 201-766-0).

We have assessed this information and identified the following issue:

As explained in the Appendix on Reasons common to several requests, section 2, information based on application of QSAR (in the registration dossier and in your

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

comments on the draft decision) is rejected.

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

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

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

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

On this basis, the information requirement is not fulfilled.

3. Long-term toxicity testing on fish

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

You have adapted this information requirement using QSAR predictions in accordance with Annex XI, section 1.3.

You have provided ECOSAR v1.11 prediction for this endpoint for the analogue substance tartaric acid (EC No 201-766-0).

We have assessed this information and identified the following issue:

> As explained in the Appendix on Reasons common to several requests, section 2, information based on application of QSAR (in the registration dossier and in your comments on the draft decision) is rejected.

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

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

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

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

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

On this basis, the information requirement is not fulfilled.

Study design

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

Appendix C: 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:

(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).

(ii) One study in which an analogue substance (L-tartaric acid) was injected into the air cell or yolk of chicken eggs (1973), dose 8 mg/kg.

In your comments on the initial draft decision you provided

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

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

We have assessed this information and identified the following issues:

a) Weight of evidence

As explained under Section B.1, the sources of information (i-ii) provide 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 under Section B.1.

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

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

Conclusion

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 adaptations are 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[3] administration of the Substance.

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

In your comments on the initial draft decision you propose that, if your weight of evidence adaptation is not accepted by ECHA, the studies requested in this decision are performed using the Substance or one of the members of the Category "Tartaric acid and its salts" [i.e. tartaric acid (EC 201-766-0), sodium potassium tartrate (EC 206-156-8), potassium hydrogen tartrate (EC 212-769-1), dipotassium tartrate (EC 213-067-8), and calcium tartrate (EC 221-621-5)]. You "*request ECHA to formally accept at Decision stage [..] that the studies will be performed with one substance representative of the Category (source substance) and used for all the members of the Category (target substances)*".

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

2. Extended one-generation reproductive toxicity study

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

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).
(ii) One 150-day repeated dose toxicity study with an analogue substance (sodium hydrogen tartrate, EC no 208-400-9) in male rabbits.

Information provided in your comments on the initial draft decision

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

We have assessed this information and identified the following issues:

a) Weight of evidence

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

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

and 4) if column 2 triggers are met, also information on sexual function and fertility of the offspring, toxicity to F2 offspring, developmental neurotoxicity and/or developmental immunotoxicity.

Sexual function and fertility

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

Sources (i) provide relevant information on maintenance of pregnancy. Source (ii) provides information on histopathology of testes after 150-day exposure.

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

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

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

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

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

Furthermore, the source (ii) provides information only on male animals.

Taken together, there is limited information on histopathology of reproductive organs in male animals but no information on functional fertility (mating, fertility, gestation (length), parturition and lactation, and no reliable information on maintenance of pregnancy.

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

Toxicity to the offspring

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

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

Source (ii) and the EFSA report do not provide any information on toxicity to offspring.

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

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

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

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

Systemic toxicity

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

The sources of information (i) provide relevant information on maternal clinical signs, survival and body weights. The information is limited to a very short time period during pregnancy only. The source of information (ii) and the repeated dose studies included in the EFSA report provide relevant information on clinical signs, survival, body weights, food consumption, haematology, and organ weights and histopathology of non-reproductive organs and tissues in adult male animals.

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

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

Conclusion on weight of evidence

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

- sexual function and fertility: weight and histopathology of reproductive organs, but lacking information on functional fertility (mating, fertility, gestation (length),

parturition and lactation, and not reliable information on maintenance of pregnancy
- systemic toxicity, but the information is limited to male animals, and not reliable information on systemic toxicity during pregnancy.

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

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

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 443 study.

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

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

Conclusion

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

The specifications for the study design

Premating exposure duration and dose-level setting

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

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

Therefore, the requested premating exposure duration is ten weeks.

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

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

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

Cohorts 1A and 1B

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

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

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

In your comments on the initial draft decision you propose that, if your weight of evidence adaptation is not accepted by ECHA, the studies requested in this decision are performed using the Substance or one of the members of the Category "Tartaric acid and its salts" [i.e. tartaric acid (EC 201-766-0), sodium potassium tartrate (EC 206-156-8), potassium hydrogen tartrate (EC 212-769-1), dipotassium tartrate (EC 213-067-8), and calcium tartrate (EC 221-621-5)]. You "*request ECHA to formally accept at Decision stage [..] that the studies will be performed with one substance representative of the Category (source substance) and used for all the members of the Category (target substances)*".

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

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[6].

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

Appendix D: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[7].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[8].

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

Appendix E: Procedure

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

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

The compliance check was initiated on 20 January 2020.

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

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

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

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

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

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

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

Appendix F: List of references - ECHA Guidance[9] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[10]

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

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[12]

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

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

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

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

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

Appendix G: 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]
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[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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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.