~~Confidential~~

Helsinki, 24 November 2021

**Addressees**
Registrant(s) of 638-38-0_manganese di(acetate) as listed in the last Appendix of this decision

**Date of submission of the dossier subject to this decision**
10/12/2020

**Registered substance subject to this decision ("the Substance")**
Substance name: Manganese di(acetate)
EC number: 211-334-3
CAS number: 638-38-0

**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 below, by the deadline of ***29 February 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. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. / OECD TG 471)

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

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

3. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested below (Annex VIII, Section 8.6.1.)

4. 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

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

2. 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)

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 IX of REACH", respectively.

**Information required depends on your tonnage band**

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

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 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**

**Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.**

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

**A. Predictions for toxicological properties**

You have provided a read-across justification document in IUCLID Section 13.

You read-across between the structurally similar substances, Manganese (II) sulfate monohydrate, EC No. 232-089-9 (CAS No. 7785-87-7), manganese dichloride EC No. 231-869-6 (CAS No. 7773-01-5) and manganese dinitrate, EC No. 233-828-8 (CAS No. 10377-66-9) as source substances and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: ”*This evaluation is based on the fact that these compounds consist of manganese cations and organic anions (usually salts of organic fatty acids). Upon dissolution of these compounds the ions are liberated in the solvent*”.

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/dissociation products. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA notes the following shortcoming(s) with regards to prediction(s) of toxicological

[2] 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)

[3] 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

properties.

- *Missing supporting information*

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*"[4]. 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 bridging studies to compare properties of the Substance and source substances.

1. *Information on the formation of common compounds and impact of non-common compounds*

As indicated above, your read-across hypothesis is based on the transformation of the Substance and of the source substance(s) to a common compound(s). In this context, information characterising the rate and extent of the dissociation of the Substance and of the source substances is necessary to confirm the formation of the proposed common dissociation products and to assess the impact of the exposure to the parent compounds as well as the impact of non-common dissociation products.

You claim that "these compounds consist of manganese cations and organic anions. Upon dissolution of these compounds the ions are liberated in the solvent".

However, you have not provided experimental data to demonstrate similarity of the dissociation rates of these substances. According to the information in your dossier, some physico-chemical properties like solubility and dissociation constant are dissimilar between the target and sources substances. Degree of dissociation of the acetic acid is much lower than that of the acids that correspond the source substances (0.004 as compared with 0.51, 0.784 and 0.82). Furthermore, the solubility of Mn diacetate is lower than that of the source substances. While you claim that there is "high structural similarity" between the target and sources substances, you have not addressed the difference between the diacetate counterion in the target substance and the inorganic counterions in the source substance. Finally you have not addressed the effect of the counterion, i.e. diacetate on the availability and toxicity of manganese cation.

In the absence of this information, you have not provided supporting evidence establishing that the proposed common dissociation products are formed in a comparable rate as assumed in your read-across hypothesis; neither have you addressed the potential toxicological impact of the non-common dissociation products. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

In your comments to the draft decision, you explain that you intend to add data on the counter ions and analyse their toxicity profile in a modified read-across statement. Furthermore, you agree to discuss the effects of the counter ions on the availability and toxicity of the manganese cation. However, these data have neither been covered in your comments nor in the registration dossier under compliance check. Therefore, for this decision, the read-across justification remains inacceptable.

2. *Missing supporting information to compare toxic properties of the substances*

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

As indicated above, your read-across hypothesis is based on the assumption that the target and source substances dissociate to common compounds, which cause same type of effect(s). Due to the deficiencies identified in the previous sub-section, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

You have provided an in vitro gene mutation studies in bacteria, four non-guideline studies on cytogenicity, four repeated dose toxicity studies, one-generation reproductive toxicity studies, reproductive toxicity screening study, and non-guideline developmental toxicity study on chicken embryos, as below specified on the source substances of the read-across, while you did not provide studies on these toxic effects of the Substance.

The studies on analogue have deficiencies identified in the corresponding Appendices below. The data set reported in the technical dossier does not include relevant, reliable and adequate toxicological information on the relevant toxicological endpoints for the Substance and of the source substance(s) to support your read-across hypothesis.

In the absence of such information, you have not established that the Substance and of the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

In your comments, you have compared the acute toxicity of the source and target substances. However, acute toxicity studies cannot be used to demonstrate similarity of repeated dose and reproductive/developmental toxicity effects, because acute toxicity studies do not cover several of the relevant endpoints, which are within the scope of repeated dose and reproductive/developmental toxicity studies, such as histopathology, clinical chemistry and hematology. Therefore, for this part, the read-across justification remains inacceptable.

*3. Adequacy and reliability of source study*

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

- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

Related deficiencies are addressed under the corresponding Appendix below.

**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.

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

### 1. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII to REACH (Section 8.4.1.).

You have provided a read-across adaptation using a key study and supporting studies in your dossier:

i. Non-guideline DNA repair study, publication Nishioka (1972), with analogue substances Mn(CH3COO)2, MnCl2, Mn(NO3)2, and MnSO4, reliability 2, no GLP.
ii. Study equivalent or similar to OECD TG 471 publication Marzin (1983), with analogue substance MnSO4*H2O, reliability 2, no GLP.
iii. Study equivalent or similar to OECD TG 471 publication Mortelmans (1983), with analogue substance MnSO4*H2O, reliability 2, no GLP.

We have assessed this information and identified the following issues:

Your read-across adaptation is not considered acceptable, as explained above in the **Appendix on Reasons common to several requests.** In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:

As provided in the Appendix on reasons common to several requests, a study must have adequate and reliable coverage of the key parameters of the corresponding test guidelines, in this case OECD TG 471. The key parameters of this test guideline include:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)

In study i, the information you provided relates to a test different from the OECD TG 471, conducted on two strains of Bacillus subtilis. Therefore, the information provided does not cover key parameter(s) required by the OECD TG 471.

In your comments you explain your intention to obtain access to further OECD TG 471 studies, which have a higher Klimisch scores and were made with $MnCl_2$ and manganese hydrogen phosphate. However, an adaptation based on these studies has neither been covered in your comments nor in the registration dossier under compliance check.

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) should be performed.

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

**1. *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study**

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

ECHA understands that you have provided a read-across adaptation using a key study and supporting study/ies in your dossier:

i. Non-guideline study, publication Olivier (1982), SOS chromotest, with analogue substances KMnO4, MnCl2*4H2O and MnSO4*H2O, reliability 2, no GLP,
ii. Non-guideline study, publication McLean (1981), Fluorometric Method for Rapid Detection of DNA Strand Breaks, with analogue substance Manganous chloride, reliability 2, no GLP.

ECHA also understands that you have provided the following *in vivo* tests using a read-across adaptation under Column 2 of Section 8.4.2:

iii. Non-guideline study in Drosophila, publication Rasmuson (1985), with an analogue substance MnCl2*4H2O, reliability 2, no GLP.
iv. Non-guideline study, Comparison of clastogenicity of inorganic Mn administered in cationic and anionic forms in vivo, publication Joardar (1990), with an analogue substance manganese sulphate EC No. 232-089-9, (CAS No. 7785-87), reliability 2, no GLP.

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

Your read-across adaptation is not considered acceptable for general reasons, as explained above in the **Appendix on Reasons common to several requests**.

In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

Regarding the above information i. and ii., as already provided in the Appendix on reasons common to several requests, a study must have adequate and reliable coverage of the key parameters of the corresponding test guidelines, in this case OECD TG 471. To fulfil the information requirement, a study must be an *in vitro* chromosomal aberration test or an *in vitro* micronucleus test, conducted in mammalian cells and comply with with the OECD TG 473 or OECD TG 487 (Article 13(3) of REACH and ECHA Guidance R.7, Table R.7.7-2).

The information provided under i. and ii. is not an *in vitro* cytogenicity study in mammalian cells nor an *in vitro* micronucleus study. Therefore, the information provided does not cover the key parameter(s) required by the OECD TG 473/487.

Similarly, regarding the above information iii. and iv., a study must have adequate and reliable coverage of the key parameters of the corresponding test guidelines, in the case of Section 8.4.2, Column 2, first indent, OECD TG 474 or 475. [5][6]

Test iii. is neither a micronucleus test nor a chromosomal aberration test. The information provided does not cover specifications/conditions required by OECD TG 474/475 adequately, such as investigation of cytogenicity. Therefore, concerning this study, the requirements of

[5] ECHA Guidance R.7a, R.7.7.6.3, p.568
[6] ECHA Guidance R.7a, Table R.7.7–3, p.558

Section 8.4.2., Column 2, first indent, Annex VIII to REACH are not met.

For all these reasons, the information provided is rejected.

In your comments on the draft decision, you explain your intention to obtain access to OECD TG 473 studies, made with MnCl2 and manganese hydrogen phosphate. However, an adaptation based on these studies has not been covered in your comments, neither in the current registration dossier. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation")."

Therefore, the requirements of Section 8.4.2., Column 2, first indent, Annex VIII to REACH are not met.

To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

**2. *In vitro* gene mutation study in mammalian cells;**

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

*i. Triggering of the study*

Your dossier contains an adaptation for an *in vitro* gene mutation study in bacteria, and an adaptation for an in vitro cytogenicity study in mammalian cells or *in vitro* micronucleus study.

The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in sections A.1 and B.1 of this Appendix.

The result of the requests for information in sections A.1 and B.1 of this Appendix will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

*ii. Assessment of information provided*

You have not provided any study that corresponds the information requirement for *In vitro* gene mutation study in mammalian cells.

Your dossier does not contain any study or adaptation in accordance with column 2 of Annex VIII, Section 8.4.3. or with the general rules of Annex XI for this standard information requirement.

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provides a negative result.

In your comments to the initial draft decision you explain your intention to obtain access to Klimisch 1 OECD 476 studies on MnCl2, "if necessary". The studies were found in ECHA dissemination website. However, these studies have not been covered in your comments,

neither in the current registration dossier. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation")."

To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

**3. Justification for an adaptation of the Short-term repeated dose toxicity study (28-day) (Annex VIII, Section 8.6.1.)**

A Short-term repeated dose toxicity study (28 days) is a standard information requirement under Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

You have provided the following study:

i. A non-guideline study, with the Substance, publication Ponnapakkam (2003), reliability 2, no GLP,

In addition, ECHA understands that you have provided a read-across adaptation using the following studies:

ii. A study equivalent or similar to OECD Guideline 407, with the analogue substance Manganese (II) sulfate monohydrate publication [redacted] (1993), reliability 2, no GLP,

iii. A study equivalent or similar to OECD Guideline 453, with the analogue substance Manganese (II) sulfate monohydrate, publication [redacted] (1993), reliability 2, no GLP,

iv. A study equivalent or similar to OECD Guideline 408, with the analogue substance Manganese (II) sulfate monohydrate, publication [redacted] (1993), reliability 2, no GLP,

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

Your read-across adaptation is not considered acceptable, as explained above in the **Appendix on Reasons common to several requests.**

In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 407 or, as provided in the Appendix on reasons common to several requests, a study must have adequate and reliable coverage of the key parameters of that test guidelines. The following key parameter(s) of this test guideline include, among others

1. dosing of the Substance daily for a period of 28 days until the scheduled termination of the study
2. examination of the animals for weight and histopathology (including thyroid gland/ thyroid hormone measurements)

The study i. does not fulfil the criterion set in OECD TG 407, because only urinary tract is examined.

The study ii. you have provided does not have the required exposure duration of 28 days as

required in OECD TG 407, because you indicated an exposure duration of 14 days that does not fulfil the criterion set in OECD TG 407.
Based on the above, the information you provided do not fulfil the information requirement.

Column 2 of Annex VIII, Section 8.6.1. provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Section C.1). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted.

Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

In your comments on the initial draft decision, you agree to submit an additional justification.

**4. Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)**

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

ECHA understands that you have provided a read-across adaptation using the following studies:

i. A study equivalent or similar to OECD Guideline 451, chronic toxicity/ carcinogenicity study, with the analogue substance Manganese (II) sulfate monohydrate, publication [redacted] (1993), reliability 2, no GLP
ii. A study equivalent or similar to OECD Guideline 421, with the analogue substance Manganese (II) sulfate monohydrate, publication Jarvinen (1975), reliability 2, no GLP
iii. A study equivalent or similar to OECD Guideline 415, with the analogue substance Manganese sulfate, publication Dorman (2005), reliability 2, no GLP.
iv. A study equivalent or similar to OECD Guideline 421, with the analogue substance Manganese chloride, publication Elbetieha (2001), reliability 2, no GLP.

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

Your read-across adaptation is not considered acceptable, as explained above in the **Appendix on Reasons common to several requests.**

In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

As provided in the Appendix on reasons common to several requests, a study must have adequate and reliable coverage of the key parameters of the corresponding test guidelines, in this case OECD TG 421 or OECD TG 422. These include for example

- Highest dose level should aim to induce toxic effects
- At least 10 male and 12-13 female animals for each test and control group
- 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
- 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.

In study ii., the highest dose level in the study did not induce any toxicity and you have not shown that the aim was to induce toxicity. Therefore, the dose level selection was too low. Furthermore, in that study male rats were not treated and therefore, the statistical power and scope of the information provided is not sufficient because it does not fulfil the criterion of at least 10 male and 12-13 female animals for each test group. Finally, this study does not have a required exposure duration according to OECD TG 421 because the exposure does not cover at least 13 days of lactation. Therefore, this study does not fulfil the criteria set in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

In study i. you have provided, investigations for parameters for sexual function and fertility such as those for mating and fertility, duration of gestation, parturition, lactation and weight, and investigations for duration of gestation/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 have not been performed as required in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

In studies ii. and iv., post-partum observation is missing, the gross pathology was performed only partly and therefore, these studies have not been performed as required in EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

In your comments on the draft decision, you correctly point out that according to REACH Annex VIII column 2, this study does not need to be conducted if a pre-natal developmental toxicity study (Annex IX, 8.7.2) or an Extended One-Generation Reproductive Toxicity Study (B.56, OECD TG 443) (Annex IX, section 8.7.3) or a two-generation study (B.35, OECD TG 416) is available, and that ECHA request a pre-natal developmental toxicity study in this decision. At present, however, no relevant study made with the Substance has been included in your dossier.

Furthermore, you explain your intention to obtain access to two-generation studies, made with MnCl2, and to a pre-natal developmental toxicity study (B.31) made with acetic acid.

However, these studies have neither been covered by your comments nor by information in the registration dossier under compliance check. Moreover, these studies are made with read-across source substances, and as explained above in the **Appendix on Reasons common to several requests**, the read-across is considered inacceptable. Concerning acetic acid, you have not provided any read-across justification that concerns this information requirement. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation")."

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

*Information on study design*

A study according to the test method OECD TG 421 or OECD TG 422 must be performed in rats with oral[7] administration of the Substance.

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

**Appendix C: Reasons to request information required under Annex IX of REACH**

**1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)**

A Sub-chronic toxicity study (90 day) is a standard information requirement under Annex IX to REACH.

You have provided the following study:

i. A non-guideline study, with the Substance, publication Ponnapakkam (2003), reliability 2, no GLP,

In addition, ECHA understands that you have provided a read-across adaptation using the following studies:

ii. A study equivalent or similar to OECD Guideline 407, with the analogue substance Manganese (II) sulfate monohydrate publication [redacted] (1993), reliability 2, no GLP,

iii. A study equivalent or similar to OECD Guideline 453, with the analogue substance Manganese (II) sulfate monohydrate, publication [redacted] (1993), reliability 2, no GLP,

iv. A study equivalent or similar to OECD Guideline 408, with the analogue substance Manganese (II) sulfate monohydrate, publication [redacted] (1993), reliability 2, no GLP,

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

Your read-across adaptation is not considered acceptable, as explained above in the **Appendix on Reasons common to several requests.**

In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408 or, as provided in the Appendix on reasons common to several requests, a study must have adequate and reliable coverage of the key parameters of that test guidelines. The following key parameter(s) of this test guideline include, among others

1. At least 10 female and 10 male animals should be used at each dose level (including control group)
2. dosing of the Substance daily for a period of 90 days until the scheduled termination of the study
3. pathology of sexual (male and female) organs, full detailed gross necropsy and subsequent histopathology of the organs specified in OECD TG 408

The study i. does not fulfil the criterion set in OECD TG 408, because only urinary tract is examined, and only six animals per dose group were used for the histopathological examination of urinary tract including kidneys. Furthermore, this study does not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 63 days that does not fulfil the criterion set in OECD TG 408.

The study ii. you have provided does not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 14 days that does not fulfil the criterion set in OECD TG 408.

In your comment, you refer to two [redacted] studies, i.e. OECD TG 408 and TG 453 made with manganese (II) sulfate monohydrate, which are included in your dossier. Furthermore, you explain your intention to provide a properly justified read-across. However, an improved read-across justification is not included in your comments. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation")."

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

*Information on the design of the study to be performed*

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the Substance is solid and according to the granulometry information it is without a significant proportion (>1% on weight basis) of particles of inhalable size.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance

**2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in one species**

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

ECHA understands that you have provided a read-across adaptation using the following studies

i. A study equivalent or similar to OECD Guideline 415, One-Generation Reproduction Toxicity Study (before 9 October 2017), publication Dorman (2005) with the analogue substance Manganese sulfate, reliability 2, no GLP

ii. A non-guideline developmental toxicity study on chicken embryos, with the analogue substance Manganese (II) acetate and Manganese sulfate, publication Verret (1990), reliability 2, no GLP.

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

Your read-across adaptation is not considered acceptable, as explained above in the **Appendix on Reasons common to several requests.**

In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

As provided in the Appendix on reasons common to several requests, a study must have adequate and reliable coverage of the key parameters of the corresponding test guidelines, in this case OECD TG 414. This include for example the following:

- investigation of external, skeletal and visceral malformations and variations has to be investigated as described in OECD TG 414.
- 20 female animals with implantation sites for each test and control group,
- examination of the dams for weight and histopathology of the thyroid gland/thyroid hormone measurements/gravid uterus weight/uterine content/body weight of the dams/clinical signs of the dams,

You have not provided information following OECD TG 414. Instead, you have provided a One-Generation Reproduction Toxicity Study (OECD TG 415) and a non-guideline study. These studies does not inform on skeletal and visceral malformations and variations as required by OECD TG 414.

In study ii. maternal animals were not exposed to the test substance. In addition in study ii., the weight and histopathology of the thyroid gland has not been examined in dams, thyroid hormone measurements have not been conducted in dams, gravid uterus weight has not been measured, uterine content has not been examined, body weights of the dams, and clinical signs of the dam were not examined as required in OECD TG 414.

In your comments on the draft decision, you refer to Klimisch 2 study according to OECD 414 on MnCl2, and a Klimisch 2 study similar to EU method B.31 on acetic acid. The studies were found in ECHA dissemination website. However, the study summaries of these studies have not been covered in your comments, neither in the current registration dossier. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation")."

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[8] administration of the Substance.

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

## 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[9].

### 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[10].

[9] https://echa.europa.eu/practical-guides
[10] 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 3 November 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 F: List of references - ECHA Guidance[11] 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)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[12]

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[13]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

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

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

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

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

**Appendix G: Addressees of this decision and their corresponding information requirements**

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

| Registrant Name | Registration number | Highest REACH Annex applicable to you |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

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.