~~Confidential~~

Helsinki, 24 November 2021

Addressees
Registrant(s) of 946-400-7_HGAMn as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
13/02/2018

Registered substance subject to this decision ("the Substance")
Substance name: Reaction products of sodium glucoheptonate with manganese sulfate and sodium hydroxide
EC number: 946-400-7
CAS number: NS

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 ***1 March 2023***.

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

2. Skin sensitisation (Annex VII, Section 8.3.)
   - *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (EU B.71/OECD TG 442E)(Annex VII, Section 8.3.1.); and
   - Only if the *in vitro/in chemico* test methods specified under point i.) are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429).

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. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below

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

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

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

Information required depends on your tonnage band

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

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

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

How to comply with your information requirements

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

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on Reasons common to several requests

1. **Assessment of 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.
- Skin sensitisation (Annex VII, Section 8.3.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

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

Grouping of substances and read-across approach

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

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 sulphate monohydrate, EC No. 918-733-8, manganese sulphate, EC No. 232-089-9, manganese chloride, EC No. 231-869-6, Manganese dioxide, EC No 215-202-6, manganese acetate, EC No. 211-334-3, D-glucono-1,5-lactone, EC No. 202-016-5, sodium gluconate, EC No. 208-407-7, as source substances and the Substance as target substance.

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 properties.

[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

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 toxicokinetic information on the formation of the common compound and bridging studies to compare properties of the Substance and source substances

1. *Information on the formation of common compound 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 biotransformation/dissociation of the Substance and of the source substances is necessary to confirm the formation of the proposed common products and to assess the impact of the exposure to the parent compounds as well as the impact of non-common dissociation products.

In IUCLID section 7.5. you explain that "*The underlying hypothesis for the read-across is that glucoheptonates and gluconates, structurally similar sugar-like carbohydrate metal-complexes, share the same metabolism pathways in mammals (they are oxidized by pentose phosphate pathway) and that their possible toxicity is a function of the metal cation rather than of the gluconate or glucoheptonate anion. Therefore, data on manganese sulfate, manganese acetate and gluconates and derivatives were taken into account to assess the repeated-dose toxicity of manganese glucoheptonate.*"

However, you have not provided experimental data on the formation of common compounds required to demonstrate rapid and complete conversion to common compounds, and without exposure of the organism to the parent compound and non-common compounds. Finally, you have not addressed the effect of the counterion, i.e. glucoheptonate on the uptake, bioavailability and toxicity of manganese cation.

In the absence of this information, you have not provided supporting evidence in your dossier establishing that the proposed common biotransformation/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 on the draft decision you state that "*as all tests (with Mn sulfate and Mn chloride) are performed with aqueous solutions, it is clear that the salts are present as the dissociated forms in highest achievable concentrations. It is also commonly known that the non-common compounds, the acetate and chloride counter-ions, are of negligible toxicity and of minor relevance for the toxicological behaviour of the manganese salt. Nevertheless, the registrant agrees to include information on this in a revised Read-across statement… This underlines that the assumption of all manganese occurring as free ions is a clear worst case approach*."

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

We agree that concerning the dissociation to Mn-cation, the source substances may represent a worst-case. However, the uncertainty of a potential effect of the heptagluconate counterion on the toxicokinetics (in particular, distrubution to the target organs) has not been addressed with substance-specific/experimental data.

Moreover, on this issue you provided the following comment: "*Further in the draft decision it is stated that the registrant has not addressed the effect of the counterion, i.e. glucoheptonate on the uptake, bioavailability and toxicity of manganese cation. The registrant understands this point. However, in his opinion also here a worst-case approach is followed when considering that the whole amount of the registered substance occurs in its dissociated form. If some manganese ions remain chelated they will be less bioavailable. There will be less exposure to free manganese and less toxicity. Thus, also regarding this point, a worst-case approach is followed by regarding the substance as being fully dissociated*."

However, you have not addressed the amount of the manganese that remains chelated, and to what extent manganese remains bound to the heptagluconate counterion in case it is in chelated form. Such chelation may lead to carrier effects by which the cation is masked and reaches tissues that were not accessible through its ionised form.

In summary, we find that there are uncertainties in the dissociation rate of the Substance and in the toxicokinetics of the substance and the effect of the heptagluconate counterion and chelated form to the kinetics. Therefore, the confidence/robustness of the read-across that you have proposed is not considered adequate.

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

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 in vivo skin sensitisation studies, in vitro gene mutation studies in bacteria, a cytogenicity study, several repeated dose toxicity studies, a one-generation reproductive toxicity study, and a screening study for reproductive/developmental toxicity, as specified below on the source substances, while you did not provide studies on these toxic effects of the Substance.You have provided studies with source substances, but not the target substance on the relevant endpoints. Therefore, 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 pointed out that "*the constituents* [redacted] *and* [redacted] *is sufficiently addressed by data on gluconates in the dossier and could be extended by real data from the sodium glucoheptonate dossier (CAS 31138-65-5). Thus, apart from Mn2+ ions, there are no further toxicological relevant compounds included in the registered substance. Nevertheless, the registrant agrees to include more detailed information on this in a revised Read-across statement.*"

We note, however, these data are not provided in your comments. ECHA acknowledges your intentions to improve the (eco)toxicological profile of the Substance and your plans to refine your read-across approach. As indicated in your comments, this strategy relies essentially on data which is yet to be generated, therefore no conclusion on the compliance can currently be made. 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")."

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.).

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

i) Bacterial Reverse Mutation Assay, OECD Guideline 471 (supporting study), with an analogue substance, manganese sulphate monohydrate, EC No. 918-733-8, reliability 2, GLP not specified, performed in 1986

ii) Bacterial Reverse Mutation Assay, OECD Guideline 471 (supporting study), with an analogue substance, manganese sulphate, EC No. 232-089-9 (CAS No. 7785-87-7), reliability 2, GLP not specified, performed in 1985.

iii) A non-guideline in vitro DNA damage and/or repair study with $Mn(CH_3COO)_2$; $Mn(NO_3)_2$; $MnCl_2$; $MnSO_4$, reliability 2, GLP not specified, performed in 1975,

iv) A non-guideline in vitro DNA damage and/or repair study with manganese chloride, EC No. 231-869-6 (CAS No. 7773-01-5) reliability 2, GLP not specified, performed in 1982

v) A non-guideline in vitro DNA damage and/or repair study with manganese chloride, manganese sulfate and KMnO4, reliability 2, GLP not specified, performed in 1997

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

The read-across that you propose is rejected as explained above in **Appendix on Reasons common to several requests.**

In addition, we have identified the following deficiency:

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[5] (1997). The key parameters of this test guideline include:

a) Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation.
b) 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)
c) The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.
d) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

The reported data for the studies i) and ii) you have provided did not include:
a) two separate test conditions, but only in absence of metabolic activation,
b) results for the appropriate 5 strains.

[5] ECHA Guidance R.7a, Table R.7.7–2, p.557

The studies iii, iv and v you have provided are not Bacterial Reverse Mutation Assays, and did not include:

c) a positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
d) a negative control with a number of revertant colonies per plate inside the historical control range of the laboratory.

Therefore, the information provided is rejected

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

In your comment to the draft decision you agree to perform the test as required.

Study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

2. Skin sensitisation (Annex VII, Section 8.3.)

Skin sensitisation is an information requirement under Annex VII to REACH (Section 8.3.). Under Section 8.3., Column 1, the registrants must submit information allowing (1) A) a conclusion whether the substance is a skin sensitiser and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and (2) risk assessment, where required.

We understand that you have provided a read-across adaptation based on *in vivo* studies, based on which you conclude that the Substance is not a skin sensitiser:

i. in vivo Local Lymph Node Assay OECD TG 429, with manganese chloride, EC No. 231-869-6, (CAS No. 7773-01-5), reliability 2, GLP not specified, performed in 1999.

ii. in vivo Local Lymph Node Assay equivalent or similar to OECD TG 429, with manganese chloride, EC No. 231-869-6 (CAS No. 7773-01-5), reliability 2, GLP not specified, performed in 1992.

iii. Human patch tests, with manganese dioxide, EC No 215-202-6, reliability 2, no GLP, performed in 1993.

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

The read-across that you propose is not acceptable as explained above in **Appendix on Reasons common to several requests.**

On this basis, the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro/in chemico* studies (OECD TG 442C, OECD TG 442D and EU Method B.71/OECD TG 442E) are considered suitable. In case *in vitro/in chemico* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study must be performed and the murine local lymph node assay (LLNA) (EU Method B.42/OEDC TG 429) is considered as the appropriate study.

In your comment to the draft decision you state that "*The murine local lymph node assay (LLNA) would be the first-choice method for in vivo testing in accordance with Annex VII to*

Regulation (EC) No 1907/2006. The results derived with this method allow an appropriate and realistic hazard assessment."

We consider that it is in your discretion to choose LLNA in case you consider that the Substance does not fall in the applicability domain of the relevant in vitro tests.

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.).

We understand that you have provided a read-across adaptation and a weight of evidence adaptation using a study in your dossier. The only study that addresses cytogenicity is:

- A non-guideline study with an analogue substance manganese sulphate EC No. 232-089-9 (CAS No. 7785-87), reliability 2, no GLP, performed in 1990.

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

The read-across that you propose is not acceptable as explained above in **Appendix on Reasons common to several requests.**

Annex XI, Section 1.2 states that there may be sufficient weight of evidence "*from several independent sources of information*".

You have only provided one source of information.

Therefore your weight of evidence adaptation is rejected.

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

Study design

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. Both are rejected for the reasons provided above.

You have provided an adaptation according to Annex XI, Section 1.5. in your dossier. In support of your adaptation you have provided in vitro studies listed in A.1 and B.1 and in addition, the following in vivo studies:

- A non-guideline study with the analogue substance manganese dichloride hydrate, reliability 2, made in 1985.
- A non-guideline study with the analogue substance manganese sulphate, EC number: 232-089-9, CAS number: 7785-87-7, reliability 2, performed in 1990.

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

The read-across that you propose is not acceptable as explained above in **Appendix on Reasons common to several requests.**

In addition, we have identified the following deficiency:

As provided in the Appendix on reasons common to several requests, a study must be have adequate and reliable coverage of the key parameters addressed in the corresponding test method, in this case OECD TG 476/490.

However, none of the studies, which you have provided is an *in vitro* gene mutation study in mammalian cells or an *in vivo* study that addresses this endpoint. The information provided does not cover the key parameter(s) required by the OECD TG 476 or 490.

The results of the request for information in sections A.1 and B.1 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.

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 provide a negative result.

In your comment to the draft decision, you agree to perform the test as required.

Study design

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. Short-term repeated dose toxicity (28 days)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement under Annex VIII to REACH.

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.5 (grouping of substances and read-across) of REACH.

In support of your adaptation, you have provided the following studies

i) A study equivalent or similar to OECD Guideline 453 with the analogue substance Manganese (II) sulfate monohydrate, EC No. 600-072-9 (CAS No. 10034-96-5), reliability 2, no GLP, performed in 1993

ii) A study equivalent or similar to OECD Guideline 408 with the analogue substance Manganese (II) sulfate monohydrate, EC No. 600-072-9 (CAS No. 10034-96-5), reliability 2, no GLP, performed in 1993

iii) A study equivalent or similar to OECD Guideline 407 with the analogue substance Manganese (II) sulfate monohydrate EC No. 600-072-9 (CAS No. 10034-96-5), reliability 2, no GLP, performed in 1993,

iv) A non-guideline study with the analogue substance Manganese acetate, EC No. 211-334-3, (CAS No. 638-38-0), reliability 2, performed in

v) A non-guideline study with the analogue substance D-glucono-1,5-lactone, EC No. 202-016-5 (CAS No. 90-80-2), reliability 2, no GLP, performed in 2004

vi) A non-guideline study for four weeks, with the analogue substance sodium gluconate, EC No. 208-407-7 (CAS No. 527-07-1), reliability 2, no GLP, performed in 2004*),.*

vii) A study equivalent or similar to OECD Guideline 407 with the analogue substance sodium gluconate, EC No. 208-407-7 (CAS No. 527-07-1), reliability 2, no GLP, performed in 2004,

viii) A non-guideline study for four weeks, with the analogue substance sodium gluconate, EC No. 208-407-7 (CAS No. 527-07-1), reliability 2, performed in 2004,

ix) A non-guideline sub chronic study, with D-glucono-1,5-lactone EC No. 202-016-5 (CAS No. 90-80-2), reliability 2, no GLP, performed in 2004.

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

As explained in the Appendix on Reasons common to several requests, your adaptation under Annex XI, Section 1.5 is rejected.

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

Information on study design

Referring to the criteria provided in Annex VIII, Section 8.6.1, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the substance is a solid, not present in particulate form.

When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/ developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[6]

Therefore the study must be performed according to the OECD TG 422, in rats and with oral administration of the Substance.

4. Screening study for reproductive/developmental toxicity

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 (Section 8.7.1), 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.

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.5 (grouping of substances and read-across) of REACH.

In support of your adaptation, you have provided seven studies with analogue substances.

[6] ECHA Guidance, Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017. (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf)

i) a non-guideline study, with the analogue substance manganese sulphate monohydrate, EC No. 918-733-8, reliability 2, performed in 1993, GLP not specified.

ii) A study equivalent or similar to OECD Guideline 421, with the analogue substance Manganese (II) sulfate monohydrate, EC No. 600-072-9 (CAS No. 10034-96-5), reliability 2, no GLP, performed in 1975 .

iii) A study equivalent or similar to OECD Guideline 415, with the analogue substance Manganese sulfate, EC No. 600-072-9 (CAS No. 10034-96-5), reliability 2, no GLP, performed in 2005 "

iv) A study equivalent or similar to OECD Guideline 421, with the analogue substance Manganese chloride, EC No. 231-869-6 (CAS No. 7773-01-5), reliability 2, no GLP, performed in 2001

v) A study equivalent or similar to OECD Guideline 407 with the analogue substance sodium gluconate EC No. 208-407-7, (CAS number: 527-07-1), reliability 2, no GLP, performed in 2004,

vi) A non-guideline study for four weeks, with the analogue substance sodium gluconate, EC No. 208-407-7, (CAS No. 527-07-1), reliability 2, performed in 2004,:

vii) A non-guideline study for four weeks, with the analogue substance sodium gluconate, EC No. 208-407-7, (CAS No. 527-07-1), reliability 2, no GLP, performed in 2004).

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

As explained in the **Appendix on Reasons common to several requests**, your adaptation under Annex XI, Section 1.5 is rejected. Furthermore, ECHA has identified the following endpoint-specific shortcomings:

As provided in the Appendix on reasons common to several requests, a study must be have adequate and reliable coverage of the key parameters addressed in the corresponding test method, in this case OECD TG 421 or OECD TG 422. The criteria of this test guideline 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, v, vi and vii, which 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.

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

In your comments to the draft decision, you point out that "… *in combination with the information derived from the available animal studies, one can conclude that manganese has no hazard for reproductive toxicity. To further support this, the registrant proposes to submit an available two-generation study according to OECD TG 416 with the source substance MnCl2*."

The information in your comments is not sufficient for ECHA to make an assessment, because, as explained in the **Appendix on Reasons common to several requests**, your adaptation under Annex XI, Section 1.5 is currently rejected. 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")."

Information on study design

When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/ developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[7]

Thus, as explained under section 3 of this Appendix a study according to the test method OECD TG 422 must be performed in rats with oral[8] administration of the Substance.

[7] ECHA Guidance, Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017. (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf)
[8] ECHA Guidance R.7a, Section R.7.6.2.3.2.

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

A. Test methods, GLP requirements and reporting

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

a) the variation in compositions reported by all members of the joint submission,
b) the boundary composition(s) of the Substance,
c) 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

a) 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.
b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

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 D: Procedure

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

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

The compliance check was initiated on 03 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 E: 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)[13]

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[14]

[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] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[14] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

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

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

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

Appendix F: Addressees of this decision and 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]

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.