SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Potassium permanganate

EC No 231-760-3

CAS No 7722-64-7

Evaluating Member State(s): France

Dated: 30 November 2018

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2017

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Potassium permanganate (EC No 231-760-3, CAS No 7722-64-7) was originally selected for substance evaluation based on following initial grounds of concern:

- Suspected Reprotoxic
- Consumer use
- Exposure of sensitive populations.

In addition, an additional concern related to genotoxicity was identified in the course of substance evaluation process.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Potassium permanganate has an EU harmonised classification (CLP00) (see section 7.6.1 for details).

In 2011, the registrants of the substance submitted a Testing proposal for a 2-generation study. This Testing Proposal was rejected considering that there was sufficient evidence to classify potassium permanganate as reprotoxic on the basis of the available one-generation study and a prenatal developmental study.

In this context, France submitted a CLH report with the proposed classification: Repro Cat. 2 for fertility (based on testicular effects and a decrease of the gestation index) and Cat. 1B for development (based on post-implantation loss and effects in pups brain).

The proposal was discussed during the RAC-39 meeting (December 2016).

Despite the effects observed, the RAC only agreed on a classification as Repro 2 for development and no classification for fertility considering that the studies available were not sufficiently reliable.

Finally, the following harmonised classification, Repr 2 – H361d, has been reported for potassium permanganate, but this classification has not yet been included in the technical adaptation to the CLP Regulation (ATP) at the time of writing this conclusion document.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION **Conclusions**	**Tick box**
Need for follow-up regulatory action at EU level	x
Harmonised Classification and Labelling	x
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures - Compliance check (CCH) - France recommends that a unique and agreed short-term OEL should be set in the European Union - France recommends that the registrants take actions without delay to update their dossiers on up to date information on use and exposure to ensure that downstream users get the appropriate advice	x
No need for regulatory follow-up action at EU level	

Following the substance evaluation, no information was requested. The concerns are clarified.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Following ECHA Member State Committee conclusion on the rejection of the testing proposal for a 2-generation reproductive toxicity study and on the need of a harmonized classification, a CLH report was submitted by France for reproductive endpoint in 2015, with a proposal to classify the substance as Repro 1B – H360Df. This proposal was discussed during the RAC 39 (December 2016). Finally, RAC proposed the harmonised classification Repr 2 – H361d considering that a more strict classification is not possible based on the poor quality of the available reproductive studies. Following this RAC conclusion and in order to check if a stricter classification would be justified, FR-MSCA proposed to include this substance on the Corap list.

During the evaluation period, the initial concern relative to effects on fertility and developmental toxicity has been clarified and the classification as Repr. 2 – H361d is considered appropriate. No further investigation is considered needed at this time.

However, based on the available data assessed in this substance evaluation, the FR-MSCA considers that the current EU harmonized classification of potassium permanganate should be updated for the following endpoints:

- Update the current Acute Tox 4* classification – H302;
- Add Skin Corr. 1C – H314;
- Add STOT RE 2 - H373 (brain).

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

/

4.1.3. Restriction

/

4.1.4. Other EU-wide regulatory risk management measures

FR-MSCA noted that the registration dossiers may not be fully compliant with the requirements of the REACH regulation regarding description of uses and related conditions of use. Users of potassium permanganate may therefore not be informed adequately on the ways to use the substance safely.

- Consumer uses have been removed from the Lead registration and one co-registration dossier, and are now advised against. However, the other co-registrant still supports consumers uses but does not provide any assessment to demonstrate how safe use can be achieved.
- There are inconsistencies in the way uses are reported in the registration dossiers (IUCLID section 3.5) and in the way they are reported and assessed in the chemical safety report (sections 2 and 9), regarding sectors of end-uses (SU), product categories (PC), process categories (PROC) and environmental release categories (ERC). FR-MSCA could not determine if these are inconsistencies/errors or if these are actual uses that have not been assessed by the registrants. In addition, differences are observed between risk management measures (RMMs) reported in different parts of the dossier (CSR part A, part B(9),the CSR, and guidance on safe use).
- In the jeans bleaching scenario, some contributing scenarios (mixing and loading of potassium permanganate and maintenance and cleaning) are missing and should be included in the exposure scenario to describe the use properly and demonstrate safe use.
- The gloves material, thickness and breakthrough time is not given in the CSR nor in section 11 of the registration dossier.
- Most exposure scenarios only address use of the solid form of potassium permanganate, but not of the aqueous solution, although workers may also use aqueous solution.

Due to these inconsistencies and missing scenarios, confusing and/or inappropriate information is communicated to downstream users which may prevent them from achieving safe uses. **The appropriate regulatory tool to formally address incompliances related to chemical safety assessment is compliance check (CCH) under Article 41(c). FR-MSCA strongly recommends all concerned registrants of potassium permanganate to update their dossiers without delay so as to address the issues listed above.**

- Other:

During the evaluation period, the Lead registrant informed FR-MSCA that it submitted an updated registration dossier (including an updated Chemical Safety Report) to ECHA in June 2016 by making an opt-out due to a long-standing dispute for the payment of the invoices related to the Joint Registration Dossier. This issue is out of the scope of Substance Evaluation, but may require another kind of action.

Recommendation to update of the registration dossier:

A read-across between $KMnO_4$ and other manganese compounds was proposed by the Lead registrant during the substance evaluation period. In this context, the Lead registrant

provided a rationale for the read-across and new toxicological data on $MnCl_2$ related to reprotoxicity. These data were considered during the substance evaluation, but are not included yet in the last version of the registration dossiers available. Therefore, FR-MSCA recommends the registrants to update their dossiers to include all these data.

Recommandation to set an European short-term OEL:

According to Gestis database (Gestis website, 2018), there are specific OELs (8 hours) for manganese and inorganic compounds (including potassium permanganate) set by the SCOEL: 0.2 mg/m^3 for inhalable fraction and 0.05 mg/m^3 for respirable fraction (SCOEL, 2011) based on neurological effects reported in humans. In contrast, there is no short-term limit value for European Union. It can be recommended that a unique and agreed short-term reference value (OEL) should be set in the European Union to take into account possible high peaks of exposure.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

/

5.2. Other actions

/

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Based on the available data assessed in this substance evaluation, the FR-MSCA considers that the current EU harmonized classification of potassium permanganate should be updated for the following endpoints:

- Update the current Acute Tox 4* classification – H302;
- Add Skin Corr. 1C – H314;
- Add STOT RE 2 - H373 (brain).

At the time being, FR-MSCA does not plan to submit a C&L proposal before 2020.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

In the framework of this Substance Evaluation process, all available data have been evaluated and considered in this conclusion document.

As mentioned in the justification document, potassium permanganate (EC 231-760-3, CAS 7722-64-7) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected Reprotoxicity (both fertility and development) based on effects reported for potassium permanganate and other manganese compounds and on the lack of fully adequate studies for this endpoint.
- Consumer use.
- Exposure of sensitive populations based on the reprotoxic concern and on the expected widespread exposure of consumers.

Following the meeting between FR-MSCA and the Lead registrant on the 19 of July 2017, the Lead registrant clarified the identity of potassium permanganate (location of the production site; source and origin of the substance). They also pointed out that to their knowledge there was no consumer use, nor biocides or pesticides use of potassium permanganate. In addition, the Lead registrant proposed a rationale for read-across between different manganese compounds to complete the toxicological dataset of potassium permanganate. In this aim, the Lead registrant submitted additional reproductive and developmental toxicity studies on an analaguous substance ($MnCl_2$) (see relevant section in this document).

During the evaluation period, updated registration dossiers were submitted by two of the four registrants (Lead registrant and another one respectively on the 12 of April 2018 and the 07 of March 2018).

Following assessment of data available and submitted during the substance evaluation period, FR-MSCA considers that the initial concern related to "suspected reprotoxicity" is clarified. At this time, no further information is needed related to this endpoint.

Consumer uses have been removed from the Lead registration and one co-registration dossier, and are now advised against. However, the other active co-registrant still support consumers uses but do not provide any use description nor assessment to demonstrate how safe use can be achieved. Update of the registration dossier is necessary to either provide an assessment or remove/advise against the use. If spontaneous update by the concerned registrant is not undertaken, compliance check (Article 41(c)) would be the adequate regulatory tool (rather than substance evaluation) to address such discrepancy.

Regarding "exposure of sensitive populations", since the initial concern related to reprotoxicity is clarified (classification as Repr. 2) there could be a risk if widespread consumer use was expected. However, as only one registrant currently supports consumer use but do not provide any detail at all on the use and conditions of use, it is not possible to determine whether sensitive population may be exposed. The above considerations on consumer use have to be solved first in order to be able to conclude.

In addition, an additional concern related to genotoxicity was identified in the course of substance evaluation process. However, considering a read-across approach with other manganese compounds, no further information is deemed necessary with potassium permanganate at this time.

Finally, FR-MSCA was aware during substance evaluation that CCH was affected by an opt-out of the Lead registrant.

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Read-across	Acceptable read-across between $KMnO_4$, $MnCl_2$ and $MnSO_4$. FR-MSCA recommends the registrants to update their dossiers to include this approach.
Acute toxicity	C&L process to be initiated: Update of the current EU harmonised classification as Acute Tox. 4* - H302 should be envisaged.
Corrosion / irritation	C&L process to be initiated: Add Skin Corr. 1C to the current EU harmonized classification.
Skin sensitisation	No concern identified
Repeated-dose toxicity	C&L process to be initiated: Add STOT RE 2 (brain) to the current EU harmonized classification.
Mutagenicity	Concern identified during Substance evaluation process but not substantiated based on a read-across approach
Carcinogenicity	No concern identified
Toxicity to reproduction	Fertility: Concern not substantiated based on a read-across approach. Development: The relevance of the RAC conclusion as Repro. 2 for development has been confirmed. FR-MSCA recommends the registrants to update their dossiers to include the new reproductive toxicity studies performed with $MnCl_2$.
Consumer use	The Lead registrant and one co-registrant advise against consumer use. However, the other active co-registrant still includes a consumer use in their registration dossier, but did not provide any description nor assessment. FR-MSCA considers that if a spontaneous update by the concerned registrant is not undertaken, compliance check (Article 41(c)) would be the adequate regulatory tool (rather than substance evaluation) to address such discrepancy.
Exposure of sensitive populations	The above considerations on consumer uses would have to be solved first in order to reach a conclusion related to exposure of sensitive populations.

7.2. Procedure

On 21 March 2017, the FR-MSCA began the potassium permanganate evaluation, with a particular focus on fertility and developmental toxicity.

On 19 July 2017, FR-MSCA met the Lead registrant, who informed FR-MSCA of the existence of an arbitration proceeding initiated by the Lead registrant against another registrant. Clarification on identity and consumer uses were also provided. After this meeting, the Lead registrant submitted new toxicological information related to reprotoxicity.

During the evaluation, France also identified genotoxicity as a potential new concern.

On 7 December 2017, FR-MSCA informed ECHA that it planned to write a conclusion document on the SEv of potassium permanganate.

During the evaluation period, there were several exchanges between Lead registrant, ECHA and FR-MSCA about the arbitration procedure between the Lead registrant and another registrant.

The FR-MSCA has submitted the conclusion document on potassium permanganate on the S-Circabc platform for a Member States consultation from 26th June 2018 until 05 July 2018.

No comments from other Member States were received during the consultation period.

On 30 November 2018, FR-MSCA sent the conclusion document to ECHA.

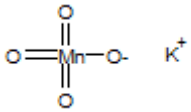
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Potassium permanganate
EC number:	231-760-3
CAS number:	7722-64-7
Index number in Annex VI of the CLP Regulation:	025-002-00-9
Molecular formula:	HMnO4.K/KMnO4
Molecular weight range:	158.03 g/mol
Synonyms:	Kálium-permanganát potasodium permanganate Potassium manganate (vii) Potassium manganate(VII) potassium manganesoylolate Potassium oxido(trioxo)manganese potassium permanganat Potassium Permanganate

Type of substance ☒Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



The compositions submitted by the registrants are considered as monoconstituent according to REACh guidance for identification and naming of substances.

All registrants have provided information on the manufacturing processes which are considered similar.

Based on the data provided initially in the dossier, the substances of the registrants can be considered as similar and have a content higher than 97%.
Regarding the impurities profile there are some differences between the registrants.

Based on the available data, none of the impurities are of concern.

Three registrants have provided IR spectra of their substance. The spectra are consistent and also concordant with standard of $KMnO_4$.
Two registrants have provided UV- spectra which are consistent.
Two registrants have provided XRD which are concordant with standard of $KMnO_4$.

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	**Key value: solid** **Dark purple or bronze-like, odourless crystals** Data from a peer review Handbook (Merck Index and CRC Lide). Data is available in literature (Kirk-otmer) which gives same result.
Melting point	**Key value: decomposition at 240°C before melting** Data from a peer review Handbooks (Merck Index and CRC Lide). Data is available in literature SAX which gives consistent result.
Boiling point	In accordance with column 2 of REACH Annex VII, Boiling point (required in section 7.3.) does not need to be conducted as the substance is decomposed before boiling.
Vapour pressure	In accordance with column 2 of REACH Annex VII, Vapour pressure (required in section 7.5.), does not need to be conducted. Potassium permanganate starts to decompose around 240°C.
Water solubility	**Key value: 76 g/L at 25°C**

	Data from a peer review Handbook (CRC Lide). Data is available in literature which gives a consistent result.
Partition coefficient n-octanol/water (Log Kow)	In accordance with column 2 of REACH Annex VII, Partition coefficient n-octanol/water (required in section 7.8.) does not need to be conducted as the substance is inorganic.
Flammability Auto-flammability	**Key value : Not flammable** The material itself is non-combustible but it will accelerate the burning of combustible material. If the combustible material is finely divided the mixture may be explosive. Contact with liquid combustible materials may result in spontaneous ignition.
Flash-point	In accordance with column 2 of REACH Annex VII, Flash point (required in section 7.9.) does not need to be conducted as the substance is inorganic. Moreover the substance is a solid
Explosive properties	**Key value : Not explosive** In accordance with column 2 of REACH Annex VII, Explosive properties (required in section 7.11.) does not need to be conducted, there are no chemical groups associated with explosive properties present in the molecule. The material itself is non-combustible but it will accelerate the burning of combustible material. If the combustible material is finely divided the mixture may be explosive. Contact with liquid combustible materials may result in spontaneous ignition.
Oxidising properties	**Key value : Strong oxidising agent** Harmonized classification Ox Sol 2 - H272
Granulometry	**Key value: D50 : 175.1 µm / D90 < 297,4 µm / D10 < 105,6 µm** Experimental data measured with ISO 13320-1 Particle size analysis – Laser diffraction methods for one registrant.
Stability in organic solvents and identity of relevant degradation products	Not required as the substance is inorganic
Dissociation constant	No need to be conducted as the substance is not stable in water. Potassium permanganate will react quickly with any organic matter in real environmental conditions.
Density	**Key value: 2,7 at 20°C** Data from a peer review Handbook (Merck Index and CRC Lide).
Viscosity	In accordance with column 2 of REACH Annex IX, Viscosity (required in section 7.17.) does not need to be conducted as the substance is solid.
Surface tension	In accordance with column 2 of REACH Annex VII, Surface tension (required in section 7.6.) does not need to be conducted as surface activity is not expected.

7.5. Manufacture and uses

7.5.1. Quantities

This substance is manufactured and/or imported in the European Economic Area in 1000 - 10 000 tonnes per year.

Table 8

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 9

USES	Use(s)
Uses as intermediate	Uncertain (ERC 6a reported, but no exposure scenario entitled "intermediate use").
Formulation	Blending, solution, repacking: ERC 2; PROC 5, 8a, 8b, 9; PC 37; substance supplied to this use as such. The following descriptors are also disseminated for formulation but do not seem to have been assessed by registrants and may not be relevant: ERC 1, 3, 6a, 6d; PROC 3.
Uses at industrial sites	Manufacture: ERC 1; PROC 2, 3, 5, 8a, 8b. The following descriptors are also disseminated for manufacture but do not seem to have been assessed by registrants and may not be relevant: ERC 2, 6a, 6c, 6d, 7. Formulation (see above) Chemical synthesis: ERC 4, 6a; PROC 2, 4, 5, 8a, 8b; SU 8, 9, 10; substance supplied to this use as such. Soil remediation: ERC 6b; PROC 5, 8a, 8b, 9; substance supplied to this use as such. Water treatment: ERC 6b; PROC 3, 5, 8a, 8b; PC 21, 37; SU 1, 2a, 4, 5, 6a, 6b, 8, 9, 10, 12, 15, 16, 18, 23; substance supplied to this use as such. The following descriptors are also disseminated under the scenario names "water treatment, oxidant" and "waste water decontamination" but do not seem to have been assessed by registrants and may not be relevant: ERC 1, 6a, 6c, 7; PROC 2.

	Jeans bleaching: ERC 6b; PROC 7; SU 5; substance supplied to this use as such. Use in alkaline oxidation: ERC 4; PROC 5, 8a, 13, 15, 28; PC 14; SU 15; substance supplied to this use as such. Some scenarios refer to "production in batch design" and "production in continuous design" which may be another name for manufacture or chemical synthesis. The following descriptors however were not included in manufacture or chemical synthesis scenarios: ERC 2, 6c, 6d, 7.
Uses by professional workers	Laboratory chemicals: ERC 8a, 8b; PROC 15; PC 21; SU 24; substance supplied to this use as such. The following descriptors are also disseminated: SU 1, 2a, 2b, 4, 5, 6a, 6b, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 23, 24. Water treatment: ERC 8b; PROC 3, 5, 8a, 8b; PC 37; SU 1, 2a, 4, 5, 6a, 6b, 8, 9, 10, 12, 15, 16, 18, 23; substance supplied to this use as such. The following descriptors are also disseminated under the scenario names "water treatment, oxidant" and "waste water decontamination" but do not seem to have been assessed by registrants and may not be relevant: ERC 1, 2, 3, 6a, 6d. Spraying water solution: ERC 8a, 8c, 8d, 8f; PROC 11; SU 1; substance supplied to this use as such.
Consumer Uses	Consumer uses are advised against by 2 registrants including the Lead registrant. But "Customer uses" are still declared by 2 other co-registrants with ERC 8a and 8b.
Article service life	-

Environmental release categories (ERC):

- ERC 1: Manufacture of the substance
- ERC 2: Formulation into mixture
- ERC3: Formulation into solid matrix
- ERC 4: Use of non-reactive processing aid at industrial site (no inclusion into or onto article)
- ERC 6a: Use of intermediate
- ERC 6b: Use of reactive processing aid at industrial site (no inclusion into or onto article)
- ERC 6c: Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article)
- ERC 6d: Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article)
- ERC 7: Use of functional fluid at industrial site
- ERC 8a: Widespread use of non-reactive processing aid (no inclusion into or onto article, indoor)
- ERC 8b: Widespread use of reactive processing aid (no inclusion into or onto article, indoor)
- ERC 8c: Widespread use leading to inclusion into/onto article (indoor)
- ERC 8d: Widespread use of non-reactive processing aid (no inclusion into or onto article, outdoor)
- ERC 8f: Widespread use leading to inclusion into/onto article (outdoor)

Process categories (PROC):

- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions
- PROC 4: Chemical production where opportunity for exposure arises

- PROC 5: Mixing or blending in batch processes
- PROC 7: Industrial spraying
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
- PROC 11: Non industrial spraying
- PROC 13: Treatment of articles by dipping and pouring
- PROC 15: Use as laboratory reagent
- PROC 28: Manual maintenance (cleaning and repair) of machinery

Product categories (PC):

- PC 14: Metal surface treatment products
- PC 21: Laboratory chemicals
- PC 37: Water treatment chemicals

Sector of end-uses (SU):

- SU 1: Agriculture, forestry and fishing
- SU 2a: Mining (without offshore industries)
- SU 2b: Offshore industries
- SU 4: Manufacture of food products
- SU 5: Manufacture of textiles, leather, fur
- SU 6a: Manufacture of wood and wood products
- SU 6b: Manufacture of pulp, paper and paper products
- SU 7: Printing and reproduction of recorded media
- SU 8: Manufacture of bulk, large scale chemicals (including petroleum products)
- SU 9: Manufacture of fine chemicals
- SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys)
- SU 11: Manufacture of rubber products
- SU 12: Manufacture of plastics products, including compounding and conversion
- SU 13: Manufacture of other non-metallic mineral products, e.g. plasters, cement
- SU 14: Manufacture of basic metals, including alloys
- SU 15: Manufacture of fabricated metal products, except machinery and equipment
- SU 16: Manufacture of computer, electronic and optical products, electrical equipment
- SU 17: General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment
- SU 18: Manufacture of furniture
- SU 19: Building and construction work
- SU 20: Health services
- SU 23: Electricity, steam, gas water supply and sewage treatment
- SU 24: Scientific research and development

Regarding the initial concern related to consumers use and exposure of susceptible populations, the Lead registrant and one of the co-registrants deleted the consumer exposure scenario during the evaluation period, and advised against these uses. However, the other active co-registrant still supports consumers uses but does not provide any use description nor assessment to demonstrate how safe use can be achieved. Update of the registration dossier is necessary to either provide an assessment or remove/advise against the use. If spontaneous update by the concerned registrant is not undertaken, compliance check (Article 41(c)) would be the adequate regulatory tool (rather than substance evaluation) to address such discrepancy.

FR-MSCA observed inconsistencies between uses reported in the registration dossiers (IUCLID section 3.5) of all registrants, and uses reported in the CSR (sections 2 and 9) of two registrants (registrant 1 and registrant 2) regarding SU, PC and ERC. In addition, co-registrants included additional ERC and PROC compared to the ones included in the Lead registrant's exposure scenarios, but whether these ERC and PROC are relevant or incorrectly reported is uncertain. However if these ERC and PROC were relevant, then the assessment would be missing from the dossiers to demonstrate safe use, since no exposure assessment and risk characterisation corresponding to these ERC and PROC are available. Also, as the exposure scenarios are communicated to downstream users (DU) *via* extended

Safety Data Sheets, these inconsistencies would lead to communicate confusing information to DU. Update of the registration dossiers is necessary to remove the inconsistencies and/or prove the missing assessments. If spontaneous update by the concerned registrants is not undertaken, compliance check (Article 41(c)) would be the adequate regulatory tool (rather than substance evaluation) to address the observed deficiencies.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 10

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
025-002-00-9	Potassium permanganate	231-760-3	7722-64-7	Oxid. Solid 2 Acute Tox 4* Aquatic Acute 1 Aquatic Chro. 1	H272 H302 H400 H410	-	-

A proposal for classification as Reprotoxic category 1B-H360Df was submitted by France in 2015. The RAC agreed in December 2016 that potassium permanganate should be classified Repr. 2 – H361d. This classification has not been included in an ATP of the CLP Regulation yet.

7.6.2. Self-classification

- In the registration(s)*:*

In the initial CSR subjected to FR-MSCA evaluation in SEV context, the Lead registrant classified potassium permanganate as:

- Skin Corr. 1C – H314
- STOT RE 2 – H373 (liver; oral)

Following exchanges between FR-MSCA and the Lead registrant, the Lead registrant proposed to change the self-classification as STOT RE 2 – H373 (liver; oral) into STOT RE 2 – H373 (brain; inhalation) by read-across with other manganese compounds such as $MnCl_2$ and $MnSO_4$.

- M factor = 10

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

- Skin Corr. 1B – H314
- Eye irrit. 2 – H319
- Aquatic chronic 3 – H412

- Carc. 1B – H350
- Muta. 2 – H341
- Repr. 2 – H361d
- Skin Irrit. 2 – H315
- STOT SE 3 – H336

7.7. Environmental fate properties

Not assessed.

7.8. Environmental hazard assessment

Not assessed.

7.9. Human Health hazard assessment

Read-across rationale

Potassium permanganate is a manganese salt of formula $KMnO_4$, composed of a K^+ cation and a permanganate anion $[MnO_4]^-$, where manganese is at its highest oxidation state, +7

Due to its oxydizing properties, $[MnO_4]^-$ would not remain in this form in the presence of organic matter. Indeed, it is expected to disintegrate into two manganese components of different valencies: Mn^{2+} and Mn^{4+} depending on the environmental condition (pH, presence of organic matter etc). The duration of this reaction phase is unknown as it depends on the physical state of the receiving body.

Under acidic conditions:

$MnO_4^- + 4H^+ + 3e^- \rightarrow MnO_2\ (s) + 2H_2O$

$MnO_4^- + 8H^+ + 5e^- \rightarrow Mn^{2+} + 4H_2O$

Under alkaline conditions, the half-reaction is (CRC, 1990):

$MnO_4^- + 2H_2O + 3e^- \rightarrow MnO_2\ (s) + 4OH^-$

Under aqueous solution, permanganic acid equilibrates with hydrogen ions in water (Willhite, 2013):

$MnO_4^- + 8H^+ + 5e^- \rightarrow Mn^{2+} + 4H_2O$

In summary, $KMnO_4$ is expected to generate MnO_2 and/or Mn^{2+} in the body. MnO_2 is considered as nearly insoluble compound. In contrast, Mn^{2+} is a systemically bioavailable form of manganese that is expected to drive the systemic toxicity of manganese compounds. Based on this assumption, the Lead registrant has defined a category with $KMnO_4$ as the target substance and Mn^{2+}, under the forms of $MnSO_4$ and $MnCl_2$, as source substances of the read-across. In particular, based on the higher water solubility of $MnSO_4$ (799 g/L at 20°C) and $MnCl_2$ (42.5 to 45.0% at 20°C) compared to $KMnO_4$ (76 g/L at 25°C), the Lead registrant considers the read-across as a worst-case approach.

It is noted that there are different valencies and chemical speciations between the target and source substances that may result into variations of toxicological properties. Relative differences in uptake, distribution and elimination as a function of chemical species (valence, solubility, particle size etc) are not available. In addition, the metabolism of manganese (specifically, the degree and the rate of oxidation state interconversions) has not been thoroughly investigated (ATSDR, 2012). Limited data suggest that manganese can undergo changes in oxidation state within the body. Under the alkaline conditions in the small intestine, Mn^{2+} is oxidized to Mn^{3+} which can be reduced in the tissues. In most

enzymes which require manganese for activity, the manganese is present in the divalent form. Mn^{2+} is considered as the most stable manganese ion which is mainly formed at pH up to pH8. In addition, reduction from Mn III or Mn IV into Mn II is favorized by microbial activity necessiting organic matter and energy. In this context, it is not expected that, once formed, Mn^{2+} is significantly converted into another manganese species in the tissues.

The available toxicological data with $KMnO_4$, $MnCl_2$ and $MnSO_4$ were compared in the following datamatrix:

	$KMnO_4$	**$MnCl_2$**	**$MnSO_4$**
EU harmonized classification	Ox. Sol. 2 – H272 Acute Tox 4* - H302 Aqua Acute 1 – H400 Aqua chronic 1 – H410 Add Repr 2 – H361d (RAC, 2017)	none	STOT RE 2 – H373** Aqua chronic 2 – H411
Acute toxicity	Oral: LD_{50} between 1090 and > 2000 mg/kg bw Dermal LD_{50} > 2000 mg/kg	Oral: LD_{50} between 200 and 1860 mg/kg	Oral: LD_{50} > 2000 mg/kg Inhalation: LC_{50} > 4.98 mg/L
Irritation/corrosion	Corrosive	No skin irritation (*in vivo* and *in vitro*)	No skin irritation (*in vivo* and *in vitro*) Eye damage *in vivo* but not irritant *in vitro* on corneal model
Skin sensitization	Not skin sensitizer	Not skin sensitizer	No reliable study
Repeated-dose toxicity study ORAL	**28-day (gavage) in rats:** From 100 mg/kg bw/day: ↓ body weight, body weight gain, food consumption, urinalysis changes At 250 mg/kg bw/day: biochemistry changes, effects on lung, stomach and rectum. Study of low quality.	No fully reliable data. Effects reported in behavioural assessment and on hematology	**14-day (diet):** no effect in mice and ↓ body weight gain in rats at 50 000 ppm (equivalent to about 5000-7500 mg/kg bw/day) **90-day (diet):** In rats: ↓ liver weight and haematological changes from 110 mg/kg bw/day In mice: ↓ liver weight and haematological changes from 330 mg/kg bw/day **2-year (diet):** In rats: ↓ survival, body weight, effect on kidney, blood, stomach, parathyroid gland, bone from 615 mg/kg bw/day in males – no effect in females In mice: effect on forestomach and thyroid from 200 mg/kg bw/day in females and 1800 mg/kg bw/day in males
Repeated-dose toxicity study	**28-day in rats:** From 300 mg/kg bw/day:	No data	No data

DERMAL	reversible local skin effects, ↓ body weight and food consumption, ↑ water consumption, changes in haematology, biochemistry and urinalysis. Study of low quality.		
Repeated-dose toxicity study INHALATION	No data	See reproductive toxicity studies	No reliable data
Genotoxicity	Inconsistent results in both *in vitro* and *in vivo*.	Negative both *in vitro* and *in vivo*.	No reliable data
Carcinogenicity	No data	No data	**2-year (diet):** In rats: no evidence of carcinogenicity at doses up to 700 mg/kg bw/day In mice: equivocal evidence of carcinogenicity: marginal increase of thyroid gland follicular cell adenoma at 2250 mg/kg bw/day
Toxicity on fertility	**One-generation study in rats (gavage):** ↓ absolute prostate weight, various damage of spermiogenesis, ↓ fertility, conception and gestation index from 320 mg/kg bw/day Systemic effects (↓ body weight) & local digestive irritation at 320 mg/kg bw/day Study of low quality.	**2-generation study in rats (inhalation):** No effect on reproduction at tested concentrations up to 20 µg/L Systemic effects (↓ body weight and food consumption) at 20 µg/L & local respiratory irritation at all tested doses (lowest tested concentration = 5 µg/L)	No relevant study
Developmental toxicity	**One-generation study in rats (gavage):** Vacuolisation of brain cell nuclei in pups in all tested groups (lowest tested dose = 20 mg/kg bw/day) From 80 mg/kg bw/day: late opening of eye. At 320 mg/kg bw/day: ↓ viability index and increase of relative and absolute brain weight of pups. Parental toxicity: systemic effects (↓ body weight) & local digestive irritation at 320 mg/kg bw/day. **Prenatal developmental toxicity study in rats (gavage):**	**2-generation study in rats (inhalation):** No effect on development at tested concentrations up to 20 µg/L **Prenatal developmental toxicity study in rats (inhalation):** Delayed ossification, wavy ribs, effects on thyroid and ↓ pup body weight at 25 µg/L. Parental toxicity: systemic effects (↓ body weight, body weight gain and food consumption) & local respiratory irritation from 15 µg/L.	No relevant study

	Delayed ossification and skeletal variations in all test all tested groups (lowest tested dose = 20 mg/kg bw/day) At 500 mg/kg bw/day: ↑ post-implantation losses and ↓ pup body weight. Parental toxicity: local digestive irritation from 100 mg/kg bw/day and ↓ body weight at 500 mg/kg bw/day. Study of low quality.	**Prenatal neurotoxicity study in rats (inhalation):** No effect on development at tested concentrations up to 25 µg/L **Non-guideline studies: exposure from birth to weaning or for the entire life in rats (oral):** Effects on nervous system development in all tested groups (lowest dose of 25 mg/kg bw/day).	

Based on the table above, $MnCl_2$ has a higher oral acute toxicity than $KMnO_4$ and $MnSO_4$. This may be due to the higher bioavailability expected for this compound.

Regarding local effects, there is a clear difference between the 3 substances with $KMnO_4$ being corrosive whereas no skin irritation has been reported for $MnCl_2$ and $MnSO_4$. Nevertheless, some findings also demonstrated irritative potential of $MnCl_2$ and $MnSO_4$. Indeed, eye damage was noted for $MnSO_4$ and respiratory irritation with $MnCl_2$ after repeated exposures. Therefore, based on this difference of potency, read-across for local effects is not considered valid between the substances considered.

Regarding systemic effects after repeated exposure, consistent general effects (biochemistry and haematology changes, decreased body weight and body weight gain), without any particular target organ identified, were reported with $KMnO_4$ and $MnSO_4$ when administrated orally (either by gavage or in the diet) for short or medium duration. Regarding genotoxicity, inconsistent results were noted for KMnO4. However the relevance of the positive results is questionable based on the limitations reported in the studies. $MnCl_2$ is not considered to be genotoxic. Concerning fertility, some effects were observed after oral administration of $KMnO_4$ in the presence of local irritation in a one-generation study of low quality. No effect on reproduction was reported in a well-performed 2-generation study with $MnCl_2$ performed by inhalation. This discrepancy can be explained by the different protocols used (e.g. selection of doses tested and exposure route etc) of different quality.

Regarding developmental toxicity, skeletal anomalies were consistently observed with both $KMnO_4$ and $MnCl_2$. Other developmental effects were also noted and were closely related to the protocol used or examination performed (foetal lethality, effects on thyroid, effects on nervous system development). Overall, similarities in the systemic toxicity have been concluded for $KMnO_4$, $MnSO_4$ and $MnCl_2$. The differences reported are considered to be either linked to the protocol used and/or to some quantitative differences of bioavailability between the three substances.

No significant toxicological impact is expected from the counter-ions: chloride for $MnCl_2$, sulphate for $MnSO_4$ or potassium for $KMnO_4$.

In summary, based on the kinetics/behaviour profile of manganese, on physico-chemical properties and similarities in the toxicological profile, FR-MSCA agrees with the proposed read-across between $KMnO_4$ and $MnSO_4$ or $MnCl_2$. This read-across is only valid when systemic effects related to Mn^{2+} are considered. This read-across does not take into account the oxidative properties of $KMnO_4$ and

thus cannot be used to estimate local effects of $KMnO_4$. This read-across corresponds to scenario 1 ((bio)transformation to common compound(s)) of the RAAF (2017).

7.9.1. Toxicokinetics

There is no data with potassium permanganate ($KMnO_4$) related to toxicokinetics. The following information is available from published reviews on manganese.

In humans and animals, manganese is an essential nutrient that plays a role in bone mineralization, protein and energy metabolism, metabolic regulation, cellular protection from damaging free radical species, and formation of glycosaminoglycans. Manganese acts as both a constituent of metalloenzymes and an enzyme activator. Enzymes that contain manganese include arginase, pyruvate carboxylase, and manganese-superoxide dismutase (MnSOD). Manganese, in its activating capacity, can bind either to a substrate (such as adenosine triphosphate, ATP), or to a protein directly, thereby causing conformational changes. Manganese has been shown to activate numerous enzymes involved with either a catalytic or regulatory function (e.g., transferases, decarboxylases, hydrolases) (ATSDR, 2012).

After ingestion, the amount of manganese absorbed is variable, but is generally considered less than 10% (and typically between 3-5% in humans) in adults (EFSA, 2013). The low oral absorption is likely due to the homeostatic control the body exerts on the amount of manganese absorbed following oral exposure to avoid an excess of manganese (ATSDR, 2012). Data are not available on the relative absorption fraction for different manganese compounds. Results from animal studies indicate that the gastrointestinal absorption of manganese is rapid and expected to be dependent of the solubility of the compound. One of the key determinants of absorption appears to be dietary iron intake, with low iron levels leading to increased manganese absorption. Phosphorus and calcium have been found to decrease manganese uptake (ATSDR, 2012).

Manganese is distributed throughout all cells in the body. It accumulates in cells rich of mitochondria. The highest concentration of manganese is found in liver, kidney, pancreas and brain (MAK, 2012).

In humans, absorbed manganese is removed from the blood by the liver where it is secreted in the bile and is excreted into the intestine and then in the feces. The enterohepatic circulation plays an important role in the maintenance of the steady-state manganese concentrations in the body (ATSDR, 2012; MAK, 2012). Very little (around 1 % of dietary intake) is excreted in the urine (EFSA, 2013). Elimination of manganese from the body is reported to vary, with a half-life between 13 and 37 days (ATSDR, 2012).

Manganese crosses the placental barrier in man and in animals, accumulates in the foetus and crosses the blood-brain barrier four times as readily in newborn babies as in adults. It is secreted in the milk. The gastrointestinal absorption of manganese is significantly more effective in infant/children than in adults (up to 40%), it is not effectively eliminated from the body and even less effectively from the brain (MAK, 2012; ANSES, 2018). Thus, foetus/infant/children are expected to be particularly sensitive to manganese exposure.

7.9.2. Acute toxicity and Corrosion/Irritation

Potassium permanganate has a harmonized classification as Acute Tox. 4* - H302 (minimal classification).

From the original C&L proposal, the data allowing classifying potassium permanganate as Xn, R22 report a LD_{50} oral in rats at 1090 mg/kg. However, the reference of this result is

not clear. Based on an *in vivo* study performed in rats equivalent to OECD 423 guideline and reported in the CSR, the LD_{50} of potassium permanganate is higher than 2000 mg/kg bw (unpublished study report 1, 2006). Finally, a median lethal dose (LD_{50}) was estimated at 1449.7 mg/kg body weight by Saganuwan *et al.* (2008) in Swiss albino mice.

Cases of human acute intoxication are reported in the literature but seems related to the corrosive properties of potassium permanganate.

Overall, the current EU harmonized minimal classification should be updated in the regards of the new available data.

The registrants concluded the substance is not acutely toxic by dermal route (LD_{50} > 2000 mg/kg bw) and based on the available information, FR-MSCA can support this conclusion.

The registrants concluded the substance is corrosive based on an *in vivo* study in which full thickness destruction of skin is reported in one rabbit (unpublished study report 2, 2006). Thus, they self-classify potassium permanganate as Skin Corr. 1C. Based on the available information, the FR-MSCA can support this conclusion. A process of harmonized classification should be initiated for this endpoint.

7.9.3. Sensitisation

The registrants concluded the substance is not sensitising based on a guinea pig maximisation test. Based on the available information, the FR-MSCA can support this conclusion.

7.9.4. Repeated dose toxicity

Only short-term toxicity studies are available with potassium permanganate.

In the first study, male and female Wistar rats (6/sex/group) were exposed to 0, 40, 100 or 250 mg/kg bw/day of potassium permanganate (purity = 99.42%; in the form of a solution in water) for 28 days by gavage (unpublished study report 3, 2006). A NOAEL of 40 mg/kg bw/day was set by the Lead registrant. FR-MSCA considers this NOAEL as conservative since the effects reported at 100 mg/kg bw/day are very slight and reversible. They include a decrease of body weight, body weight gain, food consumption, food conversion and water consumption and changes in urinalysis. Most of these effects are reversible during the 14-day recovery period or not dose-related. Statistical analysis are not always reported and historical control data are not available. This makes difficult any firm conclusion on the relevance of the findings at this dose, in particular on urinalysis. In contrast, at the highest dose, the effects are more pronounced. In addition to the above findings, changes in biochemistry (decreased protein and albumin) and an increase of histopathological findings in lung (inflammation), stomach (oedema and eosinophil infiltration) and rectum (areactive necrosis) are reported at 250 mg/kg bw/day. These effects can be related to local irritation. Based on this study, the Lead registrant self-classifies the substance as STOT RE 2 for liver effects. However, FR-MSCA questions the relevance of this self-classification since no dose-related increase of histopathological changes in the liver is noted. FR-MSCA considers this study of limited quality considering the absence of statistical analysis for all parameters and the absence of historical control data. In addition, some effects are reported in all animals of the control and treated groups (activation of haematopoiesis in bone marrow and extramedullary haematopoiesis in spleen) questioning the adequacy of the conduct of this study.

In the second study, male and female Wistar rats (5/sex/group) were exposed to 0, 150, 300 or 600 mg/kg bw/day of potassium permanganate (purity = 99.42%%; in the form of

a solution in water) for 28 days by dermal application (semi-occlusive) (unpublished study report 4, 2009). A NOAEL of 150 mg/kg bw/day was set by the Lead registrant. The FR-MSCA can agree with this NOAEL for systemic and local effects. Regarding local effects, reversible microscopical findings were noted in the skin (inflammation, parakeratosis, hyperkeratosis) from 300 mg/kg bw/day. Regarding systemic effects, decreased body weight and food consumption, increased water consumption, changes in haematology, biochemistry and urinalysis were reported at 300 mg/kg bw/day, most of them being reversible within the 14-day recovery period. However, statistical analysis are not always reported and historical data controls are not available. This makes difficult any firm conclusion on the relevance of the findings. FR-MSCA considers this study of limited quality considering the absence of statistical analysis for all parameters and the absence of historical control data. In addition, some effects are reported in most of the animals of the control and treated groups (erythrocytosis and hyperplasia in lymph nodes) questioning the adequacy of the conduct of this study.

Following exchanges between the Lead registrant and the FR-MSCA, the Lead registrant agreed with the low klimisch rating of these studies. In order to fill this endpoint, the Lead registrant proposed a read across to repeated-dose toxicity studies performed with $MnSO_4$. FR-MSCA considers the proposed read-across between $MnSO_4$ and $KMnO_4$ acceptable to estimate the systemic toxicity of $KMnO_4$. The NTP (1993) carried out 14-day, 13-week and 103-week studies with $MnSO_4$ in the diet in both rats and mice.

In the 14-day studies, there was only a decrease in body weight gain in rats and no effect in mice at the highest tested dose of 50 000 ppm (equivalent to about 5000 mg/kg bw/day in rats or 7500 mg/kg bw/day in mice, using the converting table from OECD, 2002).

In the subchronic study in rats, the only effects reported in males are a lower absolute and relative liver weight and an increase of monocytes in all exposed groups (from 1600 ppm equivalent to about 110 mg/kg bw/day). In females, there was a decrease in body weight and a reduction of leucocytes and lymphocytes at doses from 6250 ppm (equivalent to about 625 mg/kg bw/day, using the converting table from OECD, 2002).

In the subchronic study in mice, there was only a decreased body weight gain in all exposed groups of males (from 3130 ppm equivalent to about 330 mg/kg bw/day). In females, there was a decrease in body weight gain and haematological changes at 50 000 ppm (equivalent to 7500 mg/kg bw/day).

In the chronic study in rats, decreased survival, decreased body weight, nephropathy, increased mineralization of blood vessels and of glandular stomach, parathyroid gland hyperplasia, fibrous osteodystrophy of the femur were reported at an equivalent dose of 615 mg/kg bw/day in males. In females, there were no non-neoplastic lesions at the highest dose tested 15 000 ppm, equivalent to about 715 mg/kg bw/day.

In the chronic study in mice, focal hyperplasia of the forestomach epithelium with ulcer and inflammation and thyroid follicular dilatation and hyperplasia were reported in males at an equivalent dose of 1800 mg/kg bw/day. In females, a decreased body weight and focal hyperplasia of follicular epithelium in thyroid gland were reported in all exposed groups from 1500 ppm (equivalent to about 200 mg/kg bw/day).

Overall, consistent systemic effects were reported with $KMnO_4$ and $MnSO_4$ when administrated orally (either by gavage or in the diet) in studies of short- or medium-term duration. They mainly consist on effects on body weight and on haematology. When exposed for longer duration to $MnSO_4$ in the diet, additional findings were reported in various organs. Although neurological effects are well recognized as the main effects after repeated inhalation exposure manganese from human and animal data (ATSDR, 2012; Santé Canada, 2016; ANSES, 2018), the studies listed above do not report any effect related to neurotoxicity. Only the 28-day oral toxicity study performed with $KMnO_4$ included clinical and functional observations, in addition to histopathology and weight of brain. Slight decrease of grip strength of pectoral legs and pelvis legs was reported in both sexes at 250 mg/kg bw/day; this effect was reversible. In addition, in females, a reversible decreased

number of upstanding and increased number of emiction during 3 minutes of observation period was recorded at 250 mg/kg bw/day. The lack of evident neurotoxic effect in this study can be explained by the limited quality of the study and/or the too short duration of exposure. The other available studies summarized above were not specifically designed to assess neurotoxicity that might have been reported with chronic exposure to sufficiently high doses of manganese.

The permanent neurological disorder associated with manganese is indeed known as manganism.

It develops gradually, in three phases (WHO 1986 cited in MAK, 2012):

I - subclinical symptoms such as headaches, memory disorders, dizziness, weakness, tiredness;
II - gait disorders, stuttering, compulsive crying and laughing, muscle dystonia (increased tonus in resting muscles);
III - fully developed disorder with symptoms like parkinsonism, that is, with severe functional disorder of the extrapyramidal brainstem ganglia; occasionally mutilating joint disorders have been described.

Manganese can enter the brain via three pathways: (1) from the nasal mucosa to the brain olfactory bulb via olfactory neural connections; (2) from the blood through capillary endothelial cells of the blood-brain barrier; and (3) from the blood through the cerebral spinal fluid via the choroid plexuses.

There is conclusive evidence from studies in humans that inhalation to high levels of manganese compounds can Lead to manganism. ATSDR (2012) considered that subclinical neurological effects (such as deficit in tests of neuromotor or cognitive funtions and altered mood states) occurred in workers chronically exposed to about 0.07 to 0.97 mg manganese/m^3 (manganese in total or inhalable dust measurement) and that frank manganism have been associated with workplace inhalation exposure levels from about 2 to 22 mg manganese/m^3. The MAK (2012) considered that the lowest average manganese concentration which has been shown to cause slight neurotoxic symptoms was about 0.25 mg/m^3. This concentration was used as a basis for the establishment of the MAK value.

Effect of oral exposure to manganese in humans has been less investigated. Even if some publications report some associations between neurotoxicity and exposure to manganese following oral exposure, the evidence in humans is inconclusive due to several limitations noted in the studies and reports. Only one human case of neurotoxicity after accidental ingestion of $KMnO_4$ is available. One man ingested (125 mL of 8% $KMnO_4$ solution) for 4 weeks (total dose of 10 g) and began to notice weakness and impaired mental capacity after several weeks followed by a syndrome similar to Parkinson's disease after about 9 months. The authors speculated that the ingested MnO_4^- was reduced to Mn(II) or Mn(III); however, while this would be expected, it was not measured. Since MnO_4^- is a corrosive agent, it seems likely that it may have caused significant injury to the gastrointestinal tract (the patient did experience marked stomach pain), perhaps leading to a larger-than-normal gastrointestinal absorption of manganese (ATSDR, 2012). In the same way, some cases of neurotoxicity related to manganese exposure were also reported in patients with chronic hepatic disease (ANSES, 2018).

Effects on the central nervous system are also seen in animals after both ingestion and inhalation of high doses of manganese. For example, altered behaviour, lesions of the brain structure and modification of the level and/or activity of neurotransmitters were reported in repeated-dose toxicity studies by oral route with $MnCl_2$ (ANSES, 2018).

The principal mechanism in which manganese neurotoxicity occurs has not been clearly established. Many researchers consider that the manganese ion, Mn(II), enhances the autoxidation or turnover of various intracellular catecholamines, leading to increased production of free radicals, reactive oxygen species, and other cytotoxic metabolites, along

with a depletion of cellular antioxidant defense mechanisms. It has also been suggested that the mechanism of manganese neurotoxicity may in part involve complex interactions with other minerals such as Ca(II). Most mechanistic researches on manganese neurotoxicity have focused on perturbations of the dopaminergic system, but there is evidence to suggest that early consequences of manganese neurotoxicity may involve perturbations of other neurotransmitters including GABA and glutamate in the basal ganglia and other brain regions (ATSDR, 2012).

ATSDR (2012) considered that the comparison of neurological effects across species is not straightforward due to the wide dose ranges administered, the variety of responses, and the differences in measured endpoints. In particular, it is noted that characterizing behavioral changes following basal ganglia damage in rodents was difficult. In addition, although in humans and primates, the striatum, globus pallidus, and substantia nigra are the primary neurotoxicity target for manganese, rodents do not accumulate manganese in the basal ganglia (i.e., the collection of deep regions of the brain including the striatum [comprised of the caudate and putamen]) to the same relative degree. However, FR-MSCA noted that neurotoxicity is reported in both human and rodent species after exposure to manganese, considering this effect as of high concern for human health.

In addition to the brain, the lung is the other primary target organ of manganese dust reported in the literature. In humans, inhalation of particulate manganese compounds (in particular manganese dioxide and manganese tetroxide) can lead to an inflammatory response in the lung, characterized by an infiltration of macrophages and leucocytes, which, over time, can result in impaired lung function. Lung toxicity is manifested as an increased susceptibility to infections such as bronchitis and can result in manganic pneumonia (ATSDR, 2012; MAK, 2012). There was no study with $KMnO_4$ by inhalation. However, due to its corrosive properties, lung toxicity due to local effect is expected.

Based on the read-across with other manganese compounds such as $MnCl_2$ and $MnSO_4$, the Lead registrants proposed to change their self-classification from STOT RE 2 – H373 (liver; oral) into STOT RE 2 – H373 (brain; inhalation) considering the brain as the primary known target for manganese toxicity. FR-MSCA agrees with the new self-classification based on a weight of evidence from manganese compounds data. Considering this self-classification and the number of repeated-dose toxicity data available in human and animals, no further investigation is needed at this time for this endpoint.

7.9.5. Mutagenicity

Manganese is distributed throughout all cells in the body; therefore, it is able to enter germ cells (ATSDR, 2012).

The results of experimental studies performed with potassium permanganate are summarized in the following table.

Method	Results	Remarks	Reference
	***In vitro* studies**		
bacterial reverse mutation assay (e.g. Ames test) (gene mutation) S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) E. coli WP2 uvr A (met. act.: with and without) Doses: 1.5, 5, 15, 50, 100, 150 µg in 0.1 ml per plate Triplicate; 2 independent experiments EU Method B.13/14 (Mutagenicity - Reverse Mutation Test Using Bacteria) GLP	Evaluation of results: negative with metabolic activation negative without metabolic activation Test results: negative for S. typhimurium TA 1537 (all strains/cell types tested) ; met. act.: with and without ; cytotoxicity: not determined negative for S. typhimurium TA 1535 (all strains/cell types tested) ; met. act.: with and without ; cytotoxicity: not determined negative for S. typhimurium	4 (not assignable) key study experimental result Test material (IUPAC name): potassium permanganate (lack of detailed reporting on purity, protocol and results in the IUCLID summary)	unpublished study report 6, 2006
Method	**Results**	**Remarks**	**Reference**
	TA 98 (all strains/cell types tested) ; met. act.: with and without ; cytotoxicity: not determined negative for S. typhimurium TA 100 (all strains/cell types tested) ; met. act.: with and without ; cytotoxicity: yes (500 micrograms) negative for E. coli WP2 uvr A (all strains/cell types tested) ; met. act.: with and without ; cytotoxicity: not determined Untreated, solvent and positive controls valid.		

mammalian cell gene mutation assay (gene mutation) mouse lymphoma L5178Y cells (met. act.: with and without) Doses: Experiment 1: 0.78, 1.56, 3.13, 6.25, 9.38, 12.5, 18.75 and 25 µg/ml without metabolic activation 1.56, 3.13, 6.25, 12.5, 18.75, 25.0, 37.5 and 50.0 µg/ml with metabolic activation (2% S9) Experiment 2: 0.38, 0.75, 1.5, 3.0, 4.5, 6.0, 9.0 and 12 µg/ml without metabolic activation for 24 hours 1.56, 3.13, 6.25, 12.5, 18.75, 25.0, 37.5 and 50.0 µg/ml with metabolic activation (1% S9) OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test)	Evaluation of results: Ambiguous (without metabolic activation): statistically increased mutant frequency at the highest tested dose with dose response and exceeding the HCD in the second experiment (24 hour exposure). In the first experiment, some statistical increase of mutant frequencies but inside the HCD (4 hour exposure). Negative (with metabolic activation in both experiments)	2 (reliable with restriction) key study experimental result Test material (IUPAC name): potassium permanganate purity: 98.6%	unpublished study report 7, 2010
***In vivo* studies**			
micronucleus assay (chromosome aberration) rat (Wistar) male/female (5/sex) 300, 800, 1500 mg/kg b. w. (nominal in water) Single dose, oral - gavage Sampling: 24 hours for all dose levels or 48 hours for 1500 mg/kg bw EU Method B.12 (Mutagenicity - In Vivo Mammalian Erythrocyte Micronucleus Test) GLP	Test results: Genotoxicity: negative (Potassium permanganate, did not give rise to formation of micronuclei in immature erythrocytes in bone marrow of rat) (male/female) ; toxicity: yes (all of 20 animals of dose level 1500 mg/kg b.w. had mild symptoms of toxicity - piloerection and hunched posture - symptoms faded away 24 hours after application) No effect on immature/total erythrocyte ratio Positive and negative (solvent and untreated) controls valid	1 (reliable without restriction) Key study Experimental result Test material (IUPAC name): potassium permanganate purity: not stated in the IUCLID summary	unpublished study report 8, 2006

Two *in vitro* assays (an Ames test (unpublished study report 6, 2006) and a mouse lymphoma assay (unpublished study report 7, 2010) and one *in vivo* micronucleus assay (unpublished study report 8, 2006) are available with potassium permanganate. The Lead registrant considered all these tests as negative. FR-MSCA can agree with this conclusion for the Ames test. For the mouse lymphoma assay, FR-MSCA can also agree with this conclusion with metabolic activation but considers the results without metabolic activation as ambiguous based on a statistically dose-related increase of mutant frequency after 24-hour exposure in one experiment, exceeding the historical control data. Finally, for the *in vivo* micronucleus assay, FR-MSCA recognized the negative results of this study at doses up to 1500 mg/kg bw but noted the lack of evidence of sufficient bone marrow exposure.

There is a lot of data in the literature related to genotoxicity of manganese compounds (WHO, 1999; Assem *et al.,* 2011; ATSDR, 2012; MAK, 2012). In particular, Assem (2011) reviewed the mutagenicity and carcinogenicity of inorganic manganese compounds. In this review, studies performed with $KMnO_4$ but not reported by the Lead registrant are cited. $KMnO_4$ was found to be positive in TA102 without S9 with sulfuric acid or organic solvent and in TA100 with S9 with organic solvent only (De Meo et al. 1991 cited in Assem *et al.* 2011). The authors attributed the observed mutagenic activity to the generation of Mn^{2+}. Assem *et al.* (2011) considered the validity of this study uncertain. Positive result was also found in human peripheral lymphocytes with an increase of DNA damage in presence of H_2SO_4 but there was no positive control included and details are lacking (De Meo et al., 1991 cited in Assem *et al.* 2011). Moreover, treatment of FM3A cells to $KMnO_4$ for 48 hours resulted in an increase of chromosomal aberrations (mainly gaps but also some breaks and exchanges) at concentrations above 1 mM, concentrations which seem to be cytotoxic (Umeda and Nishimura, 1979 cited in Assem *et al.* 2011). *In vivo,* in a non-guideline study, Swiss albino mice were given $KMnO_4$ by oral route to assess chromosomal aberrations, micronucleus and sperm-head abnormalities (Joardar and Sharma, 1990). The duration of treatment lasted up to 21 days for chromosomal aberrations test, 2 days for micronucleus assay and 5 days (with a sacrifice after 35 days) for sperm-head abnormalities analysis. A dose-related increase in the number of breaks/cells, chromosomal aberration, sperm-head abnormalities and micronucleated PCE (polychromatic erythrocytes) and NCE (normochromatic erythrocytes) was reported. Assem *et al*. (2011) considered that the data reporting and methodological information are limited including lack of positive control. Based on these data combined with the mutagenicity results with other manganese compounds, the WHO (1999) and the ATSDR (2012) concluded that no overall conclusion can be made about the possible genotoxic hazard to humans from exposure to manganese compounds. In the same line, Assem *et al.* (2011) concluded that although there is some evidence that Mn may be a weak mutagen *in vitro* and possibly clastogenic *in vivo*, the underlying mechanisms are not clear. The positive result in TA102 strain can suggest that Mn^{2+} may potentially act as a mutagen by generating ROS. This is supported by *in vitro* studies reporting cytokine release and induction of cell signalling pathway with elemental Mn and increased GSH (glutathione) levels in rats exposed to $MnCl_2$. Other studies published in the early 1980's suggest that divalent Mn may exert a weak mutagenic activity by interacting directly with DNA and/or with DNA polymerase. Therefore, the evidence is considered insufficient to establish validity or relative significance of these mechanisms of action (Assem *et al.*, 2011).

Based on the inconsistent profile regarding genotoxicity of $KMnO_4$, FR-MSCA identified genotoxicity as a potential new concern in this Substance Evaluation. As read-across with $MnCl_2$ has been judged relevant for this dossier, data with $MnCl_2$ have been taken into account in order to clarify the concern raised for $KMnO_4$. Additional information on $MnCl_2$ from dissemination data on ECHA website was considered. Negative results were reported *in vitro* in an Ames test, a chromosomal aberration assay and a mouse lymphoma assay, all performed according to OECD guidelines. In addition, there were also negative results reported in an *in vivo* micronucleus assay in mouse exposed by oral gavage at doses up to 200 mg/kg bw/day of $MnCl_2$ (ECHA website, 2017).

In summary, considering the wide number of mutagenicity studies available, the negative results reported with $KMnO_4$ and $MnCl_2$ in guideline studies both *in vitro* and *in vivo*, the methodological limitations noted by Assem *et al*. (2011) on the positive studies with $KMnO_4$ and the lack of carcinogenicity of $MnSO_4$ at relevant doses, FR-MSCA considers that the concern identified during Substance Evaluation is clarified and no further investigation is needed at this time on this endpoint.

7.9.6. Carcinogenicity

No carcinogenicity study is available with potassium permanganate. Instead, studies with manganese sulfate monohydrate (NTP, 1993) is presented. FR-MSCA agrees with this read-across for systemic effect.

In rats, there is no evidence of carcinogenicity at doses up to 15000 ppm in the diet (equivalent to 615 mg/kg bw/day for males and 715 mg/kg bw/day for females). The NOAEL for non-neoplastic lesions is set at 200 mg/kg bw/day in males based on decreased survival, body weight, nephropathy, increased mineralization of blood vessels and of glandular stomach, parathyroid gland hyperplasia, fibrous osteodystrophy of the femur. The NOAEL for non-neoplastic lesions is set at 715 mg/kg bw/day, the highest tested dose, in females.

In male mice, there is no evidence of carcinogenicity at doses up to 15000 ppm (equivalent to 1800 mg/kg bw/day). In female mice, there is equivocal evidence of carcinogenicity at the highest tested dose of 15000 ppm (equivalent to 2250 mg/kg bw/day) based on a marginally increased incidence of thyroid gland follicular cell adenoma. The NOAEL for non-neoplastic lesions is set at 540 mg/kg bw/day in males based on focal hyperplasia of the forestomach epithelium with ulcer and inflammation and thyroid follicular dilatation and hyperplasia. No NOAEL for non-neoplastic lesions was set for females based on a decreased body weight and focal hyperplasia of follicular epithelium in thyroid gland in all exposed groups.

Considering that there is no evidence of carcinogenicity in both rats and mice except a marginal increase of a benign tumour at very high dose in female mice, FR-MSCA considers that no carcinogenic concern is raised for $MnSO_4$ and by extrapolation to $KMnO_4$.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Fertility

The following fertility study is available with potassium permanganate:

Method	Results	Remarks	Reference
One-generation study EU Method B.34 Rat (Wistar Han) male/female (10 males and 25 females/group) Oral: gavage, daily 7 days/week 0, 20, 80, 320 mg/kg body weight/day (nominal conc.) Vehicle: water Exposure: The treatment period for the males was 13 weeks (10 weeks of pre-mating and 3 weeks of mating period). Treatment period of females was at least 8 weeks (2 weeks of pre-mating, at least 1 day of mating, 3 weeks of pregnancy and 3 weeks of lactation).	NOAEL (general toxicity) (male/female): 80 mg/kg bw/day based on decreased body weight in males, inflammation and/or erosion of digestive tract in both sexes at 320 mg/kg bw/day NOAEL (reproduction) (male/female): 80 mg/kg bw/day based on decreased absolute prostate weight, various damage of spermiogenesis, decreased fertility, conception and gestation index at 320 mg/kg bw/day NOAEL (development) (male/female) < 20 mg/kg bw/day based on vacuolation of brain cell nuclei in pups. From 80 mg/kg bw/day: late opening of eyes at all doses. In addition at 320 mg/kg bw/day: decreased viability index and increase of relative and absolute brain weight of pups	2 (reliable with restriction) experimental result Test material (EC name): potassium permanganate (purity = 99.42%)	unpublished study report 9, 2008

In a one generation reproduction toxicity study performed according to EU method B.34 or OECD 415, Wistar Han rats received potassium permanganate by oral gavage at dose levels of 0, 20, 80 and 320 mg/kg bw/day (unpublished study report 9, 2008,). Males were dosed once daily for 13 weeks, beginning 10 weeks before mating and throughout the mating period. Females were dosed once daily for at least 8 weeks, from 2 weeks prior to mating, during mating and gestation periods to 3 weeks of lactation.

No mortality was found except one non-pregnant female in the highest dose group dying in the first week after mating. At 80 mg/kg bw/day, body weight and body weight gain were reduced in both sexes with a significant effect in males. This was associated with a decrease of food consumption. Sporadic dyspnea, red secretion and salivation were recorded in males more often than control and lowest dose groups, but did not affect all animals. At 320 mg/kg bw/day and since the first week of application period, dyspnea, decreased activity, red secretion around nose or eyes, rigidity, piloerection and salivation were registered in most of males. In females exposed at the same dose, dyspnea was recorded.

All males at the highest dose level showed marked changes in the digestive tract. Histopathological changes were recorded in digestive system with erosions, ulcerations and haemorrhage in the stomach mucosa or submucosa and inflammation in stomach, forestomach and duodenum.

Effects were also reported in testes, epididymides and prostate gland. Organ weight analysis revealed a statistically significant decrease of absolute weight of prostate gland at 320 mg/kg bw/day. In testes, various damages of spermiogenesis, atrophy of germinal epithelium and atrophy or decreased quantity of Leydig cells were found. In epididymides, damage of spermiocytes, vacuolar dystrophy and inflammation were reported. Signs of inflammation in prostate gland were also recorded. Among these effects, damage of spermiogenesis in testes and decreased number of spermiocytes in epididymides were increased at the highest dose, in comparison to other groups.

In females, treatment-related effect on digestive tract was also reported at 320 mg/kg bw/day. In digestive system, erosions, ulcerations and haemorrhage were observed in stomach mucosa or submucosa and inflammation (inclusive inflammatory infiltration of mucosa and/or submucosa) was diagnosed in stomach and forestomach. In ovaries, cysts and cellular hyperplasia of stroma were recorded. In uterus, cellular hyperplasia of endometrium, hydrometra and degenerative changes (atrophy of endometrium, extinction of endometrial glands, fibrosis of endometrium or atrophic epithelium in vagina) were noted. However, the effects observed seem not dose-related.

Some reproductive parameters were impaired. Number of pregnant females and number of dams bearing live pups were markedly lower at the highest dose level. Decrease of fertility index[2] and conception index[3] was detected at 320 mg/kg bw/day and decreased gestation index at the highest dose. Percentage of post-natal loss was slightly increased at the middle dose level. All other reproductive parameters were not adversely affected. Total number of pups was decreased with dose level. Number of pups per litter was slightly lower (but without statistical significance) at 320 mg/kg bw/day. Until 4th day after birth, 3 pups (from 1 dam) at the control group, 3 pups (from 3 dams) at 80 mg/kg bw/day and 4 pups (from 2 dams) at 320 mg/kg bw/day died. Until 7th day after birth, no further pup died. Until 14th day after birth, only one pup died at 320 mg/kg bw/day and until 21st day after birth, no other pup died. No differences in development of pups were observed at the dose level of 20 mg/kg bw/day. Observation of opening of eyes (until 14 day after birth) showed late opening at 80 mg/kg bw/day (2 litters out of 16 litters) and at 320 mg/kg bw/day (3 litters out of 10 litters). Although this effect might be considered as a delay of development, it was not associated with any effect on pup body weight. Examination of brain showed increased absolute and relative weight with statistical significance at 320 mg/kg bw/day. Vacuolisation of cell nuclei in cortex and/or hippocampus was more marked in all treated groups compared to control.

In conclusion regarding effects on reproduction, damages of spermatogenesis were observed in the presence of significant decreased body weight (up to 18.7%) and irritation of the digestive tract in males at the highest dose of 320 mg/kg bw/day. This effect on testes could explain the decreased number of pregnant females observed at the same dose. However, data available does not permit to identify which female mated with which male and thus cannot clearly link the decrease of pregnant females with effects on males. Furthermore, it is generally assumed that rodent males produce sperm in numbers that greatly exceed the minimum requirements for fertility (sperm production could be reduced up to 90 % without affecting fertility in Sprague-Dawley and Wistar rats). Nevertheless, only slight or moderate damages of spermiogenesis were observed and it is not clear if these effects were sufficient to impair fertility. Therefore, it cannot be excluded that the decreased fertility index was, at least partially, female dependent. At this dose of 320 mg/kg bw/day, less marked general effects were observed in females, however, 9 females out of 25 were found to be not pregnant. There was no significantly decreased body weight. Inflammation and/or erosion of stomach or forestomach was observed in 10/25 females.

[2] Fertility index (%) = no. of pregnant females x 100 /no. of females paired (according to the study report, the day 0 of pregnancy was defined as the day when sperm are found)

[3] Conception index (%) = no. of pregnant females rats x 100 /no. of females mated (from the study report)

Among these 10 females, only 4 females were not pregnant. Reciprocally, among the 9 females not pregnant, 5 females showed no effect on digestive tract. In this context, the decreased number of pregnant females cannot be considered a secondary non-specific consequence of general toxicity.

Based on these effects, FR-MSCA submitted a CLH report to classify potassium permanganate as Reprotoxic category 2 for fertility. On 9 December 2016, RAC concluded that the effects reported in the high dose group in the presence of severe toxicity are considered to be secondary non-specific consequences of parental toxicity. Also taking into account the general poor quality of the study (very limited statistical analysis, no historical data), RAC concluded that classification of potassium permanganate as Repr. 2 is not justified. According to FR-MSCA, the poor quality of the available study has justified the inclusion of potassium permanganate into the CORAP list in order to clarify if new fertility study is needed.

In addition, several reviews on toxicity of manganese compounds identify various effects on reproduction (WHO, 1999; INERIS, 2012; ATSDR, 2012; MAK, 2012; ANSES, 2018). The effects include impotence, loss of libido, impaired fertility and sperm toxicity in workers. For example, impotence and loss of libido are common symptoms in male workers afflicted with clinically identifiable signs of manganism. Impaired fertility (measured as a decreased number of children/married couple) has been observed in male workers exposed for 1–19 years to manganese dust (0.97 mg/m^3) at levels that did not produce frank manganism suggesting that impaired sexual function in men may be one of the earliest clinical manifestations of manganese toxicity. However, these data are inconclusive due to confounding factors, lack of dose-response information or contradictory results. Reproductive effects, such as sperm toxicity, degenerative changes in seminiferous tubules, post-implantation and sterility were also reported in experimental studies in particular at high tested doses and sometimes after exposure via unphysiological administration. In contrast, other experimental studies did not show any effect on reproductive parameters. In summary, it is concluded that no firm conclusions on reproductive toxicity of manganese compounds can be reached. In this line, the ATSDR (2012) concluded that additional studies in animals are needed to establish more clearly whether or not there is a human health concern.

Following exchanges between the Lead registrant and the FR-MSCA, the Lead registrant recognized the reduced Klimisch rating of this study based on excessively high doses, maternal toxicity, absence of historical data etc. In order to assess the reproductive hazard of $KMnO_4$, the Lead registrant proposed a read across to a recent 2-generation study performed with $MnCl_2$ (McGough & Jardine (2017)).

Method	Results	Remarks	Reference
2 generation study (Crl:CD®(SD)) rats 28/sex/group F0 24/sex/group F1 Inhalation nose-only; 6h/day; 7d/week Target concentrations: 0, 5, 10, 20 µg/L Gravimetric concentrations: 7, 17, 28 µg/L for F0 and 4, 11, 20 µg/L for F1	NOAEC local < 5 µg/L based on respiratory irritation in all treated groups of F0 generation. The same type of effects were reported in F1 generation from 10 µg/L. NOAEC systemic = 20 µg/L (no treatment-related statistically significant effect) Statistically signicant decreases in body weight gain and food consumption were reported in F0 males but were not consistently found in F0 females	1 (reliable without restriction) key study experimental result Test material (EC name): manganese chloride Purity = 99.0%	McGough & Jardine (2017) unpublished study report 10, 2017)

Analytical concentrations: 6, 15, 25 µg/L for F0 and 4, 10, 17 µg/L for F1 Exposure of females from F0 generation: 10 weeks prior mating + mating + gestation + lactation Exposure of females from F1 generation: 11 weeks after weaning + mating + gestation + lactation Exposure of males from F0 and F1 generations: 17 weeks, starting 10 weeks before mating OECD 416 guideline, GLP	and in F1. Some effects on organs weight were reported but were not consistently found among generations and without histopathological correlates. Thus, these effects are not considered adverse and/or treatment related. NOAEC reproductive = 20 µg/L (no treatment-related statistically significant effect) NOAEC development = 20 µg/L (no treatment-related statistically significant effect)		

A two-generation study according to OECD 416 guideline was performed with manganese chloride by inhalation. This route of exposure was chosen because the systemic bioavailability of inhaled manganese is expected to be higher than after ingestion. Indeed, a low oral absorption is likely due to the homeostatic control the body exerts on the amount of manganese absorbed following oral exposure to avoid an excess of manganese. Sprague-Dawley rats received manganese chloride as a powder aerosol by inhalation nose-only. The target concentrations were 0, 5, 10, 20 µg/L. The overall aerosol concentration aerosols were 6, 15 and 25 µg/L for the F0 generation and 4, 9 and 17 µg/L for the F1 generation. Particle size measurements indicated that test aerosol was respirable to rats (MMAD about 2 µm). Daily exposure was *ca* 6 hours, 7 days a weeks. F0 and F1 males were treated for a duration of *ca* 17 weeks. F0 and F1 females were dosed from *ca* 10 weeks until day 21 of lactation.

Blood measurement showed that the level of manganese chloride increased significantly in both males and females and were correlated to tested concentrations. The concentrations recorded prior mating and prior necropsy were comparable in all groups, indicating that no bioaccumulation is expected. Pre-treatment level in F1 generation is higher than pre-treatment level in F0 generation indicating an exposure during lactation.

Inhalation of manganese chloride was associated with microscopical findings in the respiratory tract. All F0 treated groups presented irritation of the larynx (inflammation, metaplasia, ulceration), lung (hyperplasia, inflammation), nasal cavity (hyperplasia, inflammation, degeneration, atrophy, ulceration, metaplasia of the olfactory epithelium), pharynx (hyperplasia, degeneration, inflammation, metaplasia) and trachea (metaplasia, inflammation, degeneration). In F1, irritation of the respiratory tract was reported from 10 µg/L in nasal cavity, pharynx and trachea. Based on these effects, no NOAEC can be derived.

Regarding systemic effects, a statistically significant decrease of body weight gain in F0 males was reported at 20 µg/L, associated with a reduced food consumption. No consistent effect was reported in F0 females and F1 males and females. Some effects on organ weight were recorded at different dose levels: reduced absolute brain weight and relative lung weight in F0 males, increased absolute and relative lung weight in F0 females, increased relative kidney weight and relative lung weight in F1 males and females. These effects are not consistent between generations and sexes and not associated with histopathological findings. In this context, a NOAEC of 20 µg/L

(corresponding to an analytical concentration of 25 µg/L for F0 and 17 µg/L for F1) was set for systemic toxicity.

There was no effect on oestrous cycle, mating performance, fertility, duration of gestation, litter size, sexual maturity, sperm motility, sperm count or sperm morphology and ovary follicle scoring in either generation. In F0 generation exposed to 20 µg/L, there was an increase in the number of animals losing more than 2 pups at birth[4] (2, 6, 5, 6 at 0, 5, 10, 20 µg/L) without impact on the mean birth index (86%, 80%, 84%, 90%). In F1 generation exposed to 10 and 20 µg/L, the pup survival over days 0-4 of lactation was slightly lower without a clear dose related response (88%, 94%, 78%, 86% at 0, 5, 10, 20 µg/L). In addition, at the highest dose, the group mean litter weights of F1 generation were slightly lower than the controls (420g, 432g, 407g, 391g at 0, 5, 10, 20 µg/L on day 21) but the mean pup weight in both males and females remained comparable to controls. These effects are not considered treatment-related. Thus a NOAEC of 20 µg/L (corresponding to an analytical concentration of 25 µg/L for F0 and 17 µg/L for F1) was set for reproductive and developmental toxicity.

In conclusion, no effect on reproduction is reported in a 2 generation reproductive toxicity study with manganese chloride, performed according to OECD guideline. Considering that the read-across between $MnCl_2$ and $KMnO_4$ is acceptable to estimate the systemic toxicity of $KMnO_4$ and that $MnCl_2$ does not show any effect on reproduction function in this study, no further investigation is required at this time in this substance evaluation.

Developmental toxicity

Manganese is an essential trace element and therefore is also of significance during pregnancy for bone growth and development of the inner ear and the reproductive organs in the embryo. Manganese crosses the placental barrier in man and in animals, accumulates in the foetus and crosses the blood-brain barrier four times as readily in newborn babies as in adults. It is secreted in the milk. Moreover, the gastrointestinal absorption of manganese is significantly more effective in infant/children than in adults, it is not effectively eliminated from the body and even less effectively from the brain (MAK, 2012). All the data indicate that foetus and infant/children can be particularly sensitive to the toxicity of an excess of manganese.

The following prenatal developemental toxicity study is available with potassium permanganate:

Method	Results	Remarks	Reference
Prenatal developmental toxicity study Rat (Wistar Han) females (24-25/group) oral: gavage 0, 20, 100, 500 mg/kg bw/day (nominal conc.) Vehicle: water Exposure: The females were administered daily from the 5th to the 19th	NOAEL maternal = 20 mg/kg bw/day based on erosion of digestive tract. In addition, at 500 mg/kg bw/day, there was a decrease in body weight. NOAEL developmental < 20 mg/kg bw/day based on a decreased number of ossification sites in the sternum and an incomplete ossification of cervical vertebrae.	2 (reliable with restriction) key study experimental result Test material (EC name): potassium permanganate (purity = 99.42%)	unpublished study report 5, 2009

[4] Number of animals losing more than 2 pups at birth = total pups born/no. of implantation sites

day of pregnancy. EU Method B.31	In addition, at 500 mg/kg bw/day, there was an increase of post-implantation losses and a decreased pup body weight.		

In a prenatal developmental toxicity study performed according to EU method B.31 or OECD 414, groups of Wistar Han rats received potassium permanganate by oral gavage during gestation days 5 to 19 at dose levels of 0, 20, 100 and 500 mg/kg bw/day (unpublished study report 5, 2009).

No maternal mortality was recorded. Treatment resulted in a statistically significant decrease of dam's body weight during the whole time of application at the highest dose, with lower food consumption. Effects on health condition were found in females of the two highest doses from the beginning of application to the end of the study. Maternal clinical signs such as red secreta around nostrils or eyes, piloerection, hoarse breath or dyspnea were sporadically observed at the middle dose level. These symptoms were also noted at the highest dose with cough, gibbous pose, anemia, apathy and cachexia. At this same dose, difficult administration (emesis, return of the test substance into oesophagus) and excited behaviour immediately after administration was often recorded. Decreases of absolute weight of uterus with dose dependence were recorded at all treated group. Slight decrease of relative weight of pregnant uterus was detected in all treated groups but without statistical significance or dose dependence. At 100 mg/kg bw/day, erosions of stomach mucosa were recorded in 3 females. At 500 mg/kg bw/day, more frequent occurrence of macroscopic changes mainly found in stomach (erosion, blood in content, ulceration, thickened stomach, oedematous mucosa, haemorrhage, congested mucosa) was reported. Increased number of resorptions (females without foetuses but with implantation) was recorded at the highest dose. Pre-implantation loss was slightly increased only at the middle dose and a 3 fold increase of post-implantation loss was detected at 500 mg/kg bw/day. The number of live foetuses was slightly decreased at 100 and 500 mg/kg bw/day but without dose dependency or statistical significance. Foetal body weight was decreased, with statistical significance only reported for females at the highest dose level. During internal examination, the following skeletal variations were increased with dose dependency: incomplete ossification of sternum and cervical vertebrae. Presence of unossified sacral vertebrae (absence of ossification sites) was recorded in all groups, including control group but incidence was higher in foetuses of treated females. The incidence of delayed ossification of vertebrae in the treated groups was higher than in the control group. This could be related to the slightly decreased weight of treated foetuses, which also may be due to the decrease in maternal body weight. In the study report, the alterations were not specified as variants or malformations. Nevertheless, it can be considered that all these alterations are variants except the absence of supraoccipital bone that is a malformation. Furthermore, it should be noted that malformations at the highest dose might be not clearly identified due to the high rate of post-implantation loss at this dose.

In conclusion, regarding developmental toxicity, decreased pup body weight was reported in all treated groups. This was statistically significant at 500 mg/kg bw/day in the presence of decreased maternal body weight. Skeletal variations (decreased number of ossification sites in the sternum and incomplete ossification of cervical vertebrae) were also observed in all treated groups. Finally, there was an important increase of post-implantation loss at the highest tested dose of 500 mg/kg bw/day.

The one generation study (see section 7.9.7.) can also bring additional information on developmental toxicity of $KMnO_4$. A decrease of gestation index was observed at 320 mg/kg bw/day. This corresponds to a decrease of dams bearing live pups among the pregnant females. The general maternal toxicity observed at this dose cannot explain the increase of abortions. Indeed, the decrease in body weight was lower than 5% at 320 mg/kg bw/day. Furthermore, several females showed inflammation of stomach or forestomach

but among the 5 females that aborted, only 2 animals showed this local effect on digestive tract which is thus not considered sufficiently severe to explain the abortions. This effect is also consistent with the increase of post-implantation losses and resorptions observed at 500 mg/kg bw/day in the prenatal toxicity study. At this dose, decreased body weight (between -9 to -14%) was noted and local effects on digestive tract were reported in 6 animals among the 8 females with total resorptions (females without foetuses but with implantation). Considering the severity of these effects, total resorptions cannot be sufficiently explained by the maternal toxicity. The other developmental effects reported in the one generation study consisted in a late opening of eye at 80 mg/kg bw/day and vacuolisation of cell nuclei in cortex and/or hippocampus of pups observed in all treated groups. These effects were observed in the absence of maternal toxicity or decreased pup body weight.

A classification for reproductive toxicity category 1B was proposed by FR-MSCA for developmental endpoint based on the low gestation index (64%) and high rate of post-implantation losses (42%). It can be noted that these effects were only observed at high doses (320 mg/kg bw/day in the one-generation study and 500 mg/kg bw/day in the pre-natal study). However, since these doses were not associated with an excessive parental toxicity, the effects observed at these doses were considered relevant for classification. Other developmental effects of lower severity and/or unclear relevance (late opening of eye, skeletal variation and histopathological effects on pup brain) were also reported and occurred at doses not associated with maternal toxicity. All these effects are considered relevant to humans, although no specific mode of action can be proposed from the available data. On 9 December 2016, RAC concluded that the effects in pup brain indicate severe effects on development following exposure to potassium permanganate. However, RAC recognized the limitations of the study: lack of statistical analysis and the absence of historical data. In addition, in the absence of specific developmental neurotoxicity study, RAC concluded that potassium permanganate should be classified as Repr cat. 2 for development.

In addition, several reviews on toxicity of manganese compounds identify developmental effects, and specifically neurological findings (WHO, 1999; INERIS, 2012; ATSDR, 2012; MAK, 2012; ANSES, 2018). Association between environmental exposure to manganese *in utero* or during the first years of life and developmental effects, including decreased newborn weight and impaired cognitive abilities, has been suggested from different human data. However, the data are inadequate because no causal relationship between effect and exposure can be established and due to the inability to control possible confounding factors. In experimental animals, although some studies did not report any developmental effect, other studies showed that pre or post-natal exposure to manganese was associated with external and skeletal malformations, delayed sexual maturation and neurotoxicity (including altered behaviour and modification of brain chemistry). For example, studies performed by Kern and Beaudin *(*Kern *et al. 2010 & 2011,* Beaudin *et al.* 2013 & 2017) have been considered by different internal organisms as key studies for establishing reference values for manganese by ingestion (MDH, 2012; Santé Canada, 2016; INSPQ, 2017; ANSES, 2018). In these studies, rats were exposed from birth until weaning or for entire life to $MnCl_2$ by oral route in water. Effects on nervous system development (including alteration of motor function and behavioural scores, changes in brain chemistry and histopathology) were reported in all tested groups, with the lowest dose of 25 mg/kg bw/day.

According to FR-MSCA, the poor quality of the available study with $KMnO_4$ supported by the developmental effects reported with manganese compounds have justified the inclusion of potassium permanganate into the CORAP list in order to clarify if a new prenatal developmental (including neurodevelopmental) toxicity study is needed.

Following exchanges between the Lead registrant and the FR-MSCA, the Lead registrant recognized the reduced Klimisch rating of the prenatal developmental toxicity study performed with $KMnO_4$ based on excessively high doses, maternal toxicity, absence of historic data etc. In order to assess the developmental hazard of $KMnO_4$, the Lead

registrant proposed a read across to recent prenatal developmental toxicity study and neurodevelopmental toxicity study performed with $MnCl_2$.

The following developmental toxicity studies are available with manganese chloride:

Method	Results	Remarks	Reference
Prenatal developmental toxicity study Han Wistar rat females Inhalation nose-only; flow-past system Exposure from gestation day 6 to 20; 6h/d Target concentrations: 5-15-25 µg/L Nominal concentrations: 11.2-34.6-58.4 µg/L Gravimetric concentrations: 4.7-15.1-26.0 µg/L after correction OECD guideline 414; GLP	NOAEC maternal = 5 µg/L based on clinical signs, reversible decreased food consumption, decreased (corrected) body weight and body weigh gain and microscopical findings in the lungs NOAEC developmental = 15 µg/L based on decreased fetal bw, macroscopical and microscopical findings in the thyroid and skeletal abnormalities.	2 (reliable with restriction) key study experimental result Test material (EC name): manganese chloride (purity ≥ 99%)	unpublished study report 11, 2016)
Developmental neurotoxicity study HanRcc :WIST(SPF) female rats (27/group) Inhalation nose-only; flow-past system Exposure during gestation (gestation days 6-19) and lactation (until post-natal day 20) Target concentrations: 0, 5, 15, 25 µg/L Nominal concentrations: 11.2, 34.6, 58.4 µg/L Gravimetric concentrations : 0, 3.5, 12.3, 17.6 µg/L after correction OECD guideline 426, GLP	NOAEL maternal = 12.63 µg/L based on reversible clinical signs and reversible effects on food consumption and body weight. NOAEL developmental = 17.6 µg/L based on no adverse treatment-related effects.	2 (reliable with restriction) key study experimental result Test material (EC name): manganese chloride (purity ≥ 99%)	unpublished study report 12, 2016

In a prenatal developmental toxicity study performed according to OECD guideline 414, groups of Wistar Han female rats received manganese chloride by inhalation during gestation days 6 to 20 (unpublished study report 11, 2016). The target concentrations were 5, 15 and 25 µg/L. Variations for the aerosol concentrations were noted and

considered by the authors to be due to hygroscopic properties of the test item. In this context, the authors applied a correction factor to the gravimetric concentration to take into account water adsorption. Therefore, some uncertainties remain on the level of the real exposure reported in this study. Particle size measurements indicated that test aerosol is respirable to rats (MMAD of about 2 µm).

There was no mortality. Breathing noises and dyspnea were reported in females at the two highest concentrations. In these groups, there were also a decrease in food consumption, a reduced (corrected) body weight gain and a (corrected) body weight loss (corrected body weight gain: - 5.9 g at 15 µg/L and -13.2 g at 26 µg/L), which reached statistical significance during the entire treatment period. The number of post implantation loss and the number of foetuses per dams were not affected by the treatment. Histopathological examination of the lung showed phagocytic alveolar macrophage foci and granulolymphocytic alveolar inflammation in most animals at the two highest tested concentrations. The severity and frequency of these lesions followed a dose-response relationship. Based on these effects, the maternal NOAEC is set at 5 µg/L.

There was no treatment-related effect related to external abnormalities and variations and on the sex ratio. A reduced fetal body weight (- 6.4 %) was reported at the highest tested concentration. This reduction is statistically significant only if calculated on an individual basis. An increase in the incidence of large or slightly large fetal thyroid was also noted at the highest concentration (12% of foetuses at 25 µg/L compared to 2% in the control group showing slightly large thyroid). The incidence at 25 µg/L was approximately twice as high as in the historical control group (5%). At microscopical examination, these findings were evidenced by diffuse follicular hypertrophy and/or hyperplasia at minimal to moderate degree in males and slight or moderate in females of the highest tested group. Skeletal examination showed treatment-related changes at the highest tested concentration, including incomplete or lack of ossification of cervical arch, metatarsals, caudal vertebrae and hind paw phalanges. In addition, the percentage of foetuses with one or more wavy ribs was higher in this group compared to control group (11.1% versus 0%). Based on these effects, the developmental NOAEC is set at 15 µg/L.

An additional group of non-pregnant females was included in this study to assess recovery. They were treated with the same concentrations for 15 consecutive days. Three animals per group were sacrificed after the end of the treatment and the remaining 3 females were sacrificed after 8 weeks recovery period. Breathing noise, decreased food consumption, body weight and body weight gain were also reported but were all reversible during the recovery period. There was no effect at macroscopical and microscopical examinations.

In summary, developmental effects (decreased fetal body weight, macroscopical and microscopical findings in the thyroid and skeletal abnormalities) were reported in the prenatal developmental toxicity study with manganese chloride. Overall, results from the studies performed with potassium permanganate and the prenatal developmental toxicity study with manganese chloride support the fact that the agreed classification in ECHA Risk Assessment Committee (RAC) as Repr. 2 for development is still justified for potassium permanaganate. No further investigation is considered needed at this time.

In a developmental neurotoxicity study performed according to OECD guideline 426, groups of Wistar Han female rats received manganese chloride by inhalation during gestation (days 6 to 19) and lactation (until post-natal day 20) (unpublished study report 12, 2016). The target concentrations were 5, 15 and 25 µg/L. Variations for the aerosol concentrations were noted and considered by the authors to be due to hygroscopic properties of the test item. In this context, the authors applied a correction factor to the gravimetric concentration to take into account water adsorption. Therefore, some uncertainties remain on the level of the real exposure reported in this study. Particle size measurements indicated that test aerosol is respirable to rats (MMAD less than 2 µm).

Breast milk measurement showed that the level of manganese chloride increased with increased administrated concentration which confirm the exposure of manganese via the milk. Blood measurement showed that the manganese concentration was below the lowest calibration solution in the control and low dose group (except two animals), around 1 µg/L in the mid dose group and between 1 – 2 µg/L in the high dose group.

One dam was killed in extremis on day 15 *post coitum* in the highest tested group. This dam showed breathing noises and labored breathing (highest grade) and was in a weakened condition. At the highest dose level, up to 70% of the dams showed breathing noises during the gestation period, with a frequency decreasing toward the end of the period. Mean food consumption was dose-dependently decreased from day 6 to 11 post-coitum at the two highest concentrations (-7 and -27% respectively compared to the control group) and recovered thereafter. There was no effect during lactation. Mean body weight gain was reduced at the two highest concentrations. In particular, a body weight loss up to 3% was reported within the first 5 days after treatment start in the highest tested group. Statistical significance was reached until day 17 post-coitum at the highest concentration and until day 12 post-coitum at the middle concentration. There was no effect during lactation. There was no effect on reproduction and breeding data or at macroscopical examination. The study report concluded at a NOAEC of 25 µg/L considering the reversibility of the effects observed. In contrast, FR-MSCA considered that a maternal NOAEC of 15 µg/L is more appropriate considering the frequency of the effects at the highest concentration and the dose-response relationship.

In pups, there was no treatment-related effect at external examination at first litter check, no treatment-related mortality and clinical signs. There were some variations of food consumption which reached statistical significance in males of the highest tested group; without evidence of a dose-response relationship. There were some decreases in body weight and body weight gain, only observed from day 22 post-partum to day 69 post-partum in all treated groups, without dose-dependence. No effect on developmental indices (pinna unfolding, incisor eruption, onset of coat development and opening of eyes) or on sexual maturation was reported. There was no functional/behavioural endpoints assessed during pre-weaning in contrast to OECD guideline recommendations. In particular, no complete functional observational battery (FOB) was possible for pups between days 5 to 11 post-partum due to the immature condition of the pups at this age. Instead a detailed clinical observation was performed without showing any treatment-related effect. The FOB on days 22, 35, 45 and 60 post-partum did not indicate any treatment-related effect. Punctual statistically significant effects (such as increased body temperature, grip strength, landing foot splay) were reported without linear curve. Locomotor activity and its development, assessed from day 13 until 60 post-partum, were not affected by manganese chloride. Learning and memory was demonstrated in all groups. The mean amplitude of startle response, time to maximum amplitude and habituation were not affected by treatment. There was no effect on brain (weight and macroscopical findings) on day 11, 22 or 63 post partum. No findings were noted on the length of the cerebellum and forebrain of all examined groups on day 11, 22 and 63 post-partum, except on day 63 post-partum where a slight decrease of length of cerebellum in males at the low dose and in females at the highest dose and also a increase of forebrain length in females in the mid dose were reported. However, it should be noted that many of the sections available for morphometric analysis and microscopic pathology were deemed non-assessable because of processing or sectioning artefacts. This decreases the confidence in the absence of findings reported in the brain. There was no findings in other organs assessed at macroscopical and microscopical examination on day 11, 22 and 63 post-partum. Overall, the developmental NOAEC was set at 25 µg/L.

In conclusion, no effect on neurodevelopment is reported with manganese chloride after inhalation exposure in a OECD 426 guideline study. This result is in contrast with the numerous findings reported in the literature (mostly non-guideline studies) showing effects on brain development after peri- and post-natal exposure to $MnCl_2$ by oral route in rodents. These discrepancies suggest that the occurrence of neurotoxicity after manganese exposure is highly

dependent of the study design. In addition, examinations performed in standard guideline studies may be not sensitive enough to identify the symptoms of neurotoxicity induced by manganese compounds.

Considering that the read-across between $MnCl_2$ and $KMnO_4$ is acceptable to estimate the systemic toxicity of $KMnO_4$ and that several data are available regarding neurodevelopmental toxicity of manganese, no further investigation is required at this time under this substance evaluation. The potential neurodevelopmental toxicity of $KMnO_4$ is nevertheless assumed to be covered through the classification as Repro. 2 for development agreed in 2016 by the ECHA Risk Assessment Committee (RAC).

7.9.8. Hazard assessment of physico-chemical properties

The substance is not explosive and not flammable. However, it is a strong oxidising agent with harmonized classification Ox Sol 2 - H272.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Potassium permanganate is a corrosive substance. Although there is no specific data on potassium permanganate, based on read-across with other manganese compounds, the substance is expected to induce neurotoxicity (known as manganism). In addition, effects on development are reported with potassium permanganate and other manganese compounds, such as $MnCl_2$, when rodents are exposed *in utero* and/or during pup development by oral route.

This Substance Evaluation primarily focuses on clarifying the hazards linked to reproductive toxicity and the consumer uses. Therefore, DNEL/DMEL derivation was not within the scope of this SEV. Different DNEL derivation approaches have been followed by the registrants. In particular, the Lead registrant and one co-registrant have derived DNELs for some routes of exposure and type of effects or have proposed a qualitative risk assessment based on corrosive properties of $KMnO_4$. The other active co-registrant does not provide any risk assessment in their registration dossier.

<u>Oral route:</u>

After exchanges between FR-MSCA and the Lead registrant, the Lead registrant and one co-registrant removed consumer uses and advised against these uses in their registration dossiers. The other active co-registrant still includes a consumer use in their registration dossier, but does not provide any description of this use nor assessment.

In addition, according to the registrants, the presence of potassium permanganate in the environment is not expected considering that it will probably react rapidly with oxidizable substances. It should also be noted that manganese is an essential nutrient that plays many roles in human organism.

Manganese is regulated by the Directive 98/83/EC on the quality of water intended for human consumption. According to this Directive, a reference quality value of 50 µg/L is set based on organoleptic and esthetic reasons.

Considering that consumer uses are advised against by the Lead registrant and a co-registrant, and that manganese is already regulated for its presence in water intended for human consumption, no exposure by oral route would be expected and no further risk characterization should be needed for oral exposure. However, a co-registrant still supports

a consumer use but no information is available to determine whether this use is actually relevant (considering that it is not expected and is advised against by the other registrants) and whether oral exposure could be possible. Update of the registration dossier by the concerned registrant is therefore necessary.

Dermal route:

Potassium permanganate is a corrosive substance even if there is no current harmonized EU classification for this endpoint. Therefore, appropriate personal protective equipments, such as gloves and protective clothing, should be worn to avoid skin contact. In the 28-day dermal study by dermal route available with $KMnO_4$, systemic and local effects occurred at the same tested dose of 300 mg/kg bw/day. Therefore, it is expected that wearing appropriate personal protective equipments is sufficient to avoid the occurrence of both local and systemic effects. No specific quantitative risk assessment is needed for dermal exposure.

Considering that potassium permanganate is not currently classified for its corrosive properties, FR-MSCA considers that a CLH proposal should be initiated for classifying the substance as Skin Corr. 1C in order to make mandatory the wearing of adequate protective equipement when handling the substance.

Inhalation route:

Potassium permanganate is a corrosive substance even if there is no current harmonized EU classification for this endpoint. Corrosive substances may also be irritating or corrosive to respiratory tract if there is a possibility of exposure via inhalation. Therefore, appropriate individual respiratory protective equipment, such as mask, should be worn to avoid contact with respiratory tract in case of uses exposing to inhalable fraction of $KMnO_4$ (such as spraying).

According to Gestis database (Gestis website, 2018), different occupational exposure limits (OEL) exist for manganese and inorganic compounds. In particular, there are specific OELs (8 hours) for manganese and inorganic compounds (including potassium permanganate) set by the SCOEL: 0.2 mg/m^3 for inhalable fraction and 0.05 mg/m^3 for respirable fraction (SCOEL, 2011) based on neurological effects reported in humans. There is no short-term limit value for European Union. However, there are existing short-term limit values in some countries, with the lowest reference value of 0.02 mg/m^3 in Germany.

No study is available by inhalation for potassium permanganate. Instead, there are studies available with $MnCl_2$. From the fertility and developmental toxicity studies performed with $MnCl_2$, the lowest NOAEC for systemic toxicity is 5 µg/L from the prenatal developmental toxicity study. Using default uncertainties factors set in the Reach guidance (R8), the obtained long-term DNEL for systemic effects is expected to be consistent with the OEL set by the SCOEL for respirable fraction. It can be noted that local effects occurred at the same or lower concentrations than those leading to systemic effects in the fertility and developmental toxicity studies performed with $MnCl_2$. Considering that $MnCl_2$ has lower irritative properties than $KMnO_4$, it is expected that irritation of the respiratory tract would be the most sensitive effect for $KMnO_4$ compared to potential systemic effects. Therefore, it is expected that wearing appropriate respiratory mask would prevent the occurrence of both local and systemic effects.

In summary, the availability of an European OEL and the wearing of mask due to corrosive properties of $KMnO_4$ are considered sufficient to avoid any systemic and local risks after inhalation exposure. Nevertheless, it can be recommended that a unique and agreed short-term reference value should be set in the European Union to take into account possible high peaks of exposure.

Considering that potassium permanganate is not currently classified for its corrosive properties, FR-MSCA considers that a CLH proposal should be initiated for classifying the substance as Skin Corr. 1C in order to make mandatory the wearing of adequate protective equipement when handling the substance.

Considering the above mentioned uncertainty related to the existence of a consumer use, update of the concerned registration dossier is necessary in order to either remove totally consumers uses from the registrered uses, or demonstrate safe use for all routes of exposure, taking into consideration that PPE cannot be a relevant risk management measure for consumers.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Regarding acute toxicity, an update of the current EU minimal classification as Acute Tox. 4* - H302 should be envisaged for potassium permanganate in the light of the new data available.

Regarding local effects, potassium permanganate has corrosive properties but no skin sensitisation properties. Thus, the current EU harmonized classification for potassium permanganate should be updated by adding Skin Corr. 1C.

No clear target organ was identified in 28-day toxicity studies of limited quality and performed by oral and dermal routes in rats. However, it is expected that, as other manganese compounds, potassium permanganate induces neurological effects, defined as manganism. Thus, the current EU harmonized classification for potassium permanganate should be updated by adding STOT RE 2 – H373 (brain)

Based on data on $KMnO_4$ and other manganese compounds, $KMnO_4$ is considered neither as a genotoxic nor as a carcinogenic substance.

Although the initial concern on fertility is not substantiated based on data with $MnCl_2$, the relevance of the classification Repro. 2 for development, as agreed by the RAC, is confirmed based on the potential neurodevelopmental toxicity reported in oral toxicity studies performed with $MnCl_2$.

7.10. Assessment of endocrine disrupting (ED) properties

Not specifically assessed. However, from available toxicological information, there is no concern raised for ED properties.

7.11. PBT and VPVB assessment

Not assessed.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

Workers exposure was not targeted by the Substance Evaluation and therefore no complete assessment was done.

However, during the course of the evaluation, one company involved in jeans bleaching directly contacted Anses to ask how to add "exposure of workers" as a concern to be addressed during SEv. Therefore the exposure scenario related to this use was scrutinised.

In the CSR of the Lead registrant, exposure by inhalation was estimated with the model MEASE version 1.02.01[5]. The registrant indicates that the mean particle size is approximately 85 microns and that it varies according to the required properties of the final product, but this is contradictory with the information indicated in section 7.4 of this report, and FR-MSCA was unable to confirm the appropriate value. According to MEASE documentation, the inhalation exposure estimates correspond to inhalable fraction. The maximal modelled exposure is 0.18 mg/m^3 which is slightly below the long-term OEL for manganese and inorganic compounds (including potassium permanganate) set at 0.2 mg/m^3 by the SCOEL (SCOEL, 2011) for systemic effects. However, the FR-MSCA points out that most exposure scenarios only address use of the solid form of potassium permanganate, but not of the aqueous solution, although workers may also use aqueous solution. Based on the available information, FR-MSCA is not able to determine which tasks involve handling of aqueous solutions.

The Lead registrant considered that risks related to workers exposure are adequately controlled by the wearing of gloves to avoid contact of potassium permanganate with skin, due to the corrosive properties of the substance. However, the gloves material, thickness and breakthrough time is not given in the CSR nor in section 11 of the registration dossier.

For exposure by inhalation, the Lead registrant specifies that "*When the concentration of KMnO4 dust in the working place is exceeding the DNEL, RPE* [respiratory protective equipment] *is required […]. Being exposed for > 240 min to KMnO4 per day required RPE, when exposure is < 60 min per day RPE is not required anymore*.". However, there are several exposure scenarios where the task duration is higher than 60 min and no RPE is recommended. In addition, the threshold of 60 minutes is not justified. Also, this information is not fully consistent with the RMM in Part A of the CSR which indicates "*Use dust filter mask*", and with section 11 of the registration dossier where it is indicated: "*Where risk assessment shows air-purifying respirators are appropriate use a full-face particle respirator type N100 (US) or type P3 (EN 143) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).*"

Overall, FR-MSCA is concerned that confusing information on adequate RMM could be communicated to downstream users. FR-MSCA considers that the exposure scenarios should be updated to include for each scenario one unique set of RMM with adequate PPE (gloves, protective clothes, googles, RPE) able to manage both local and systemic risk.

Update of the concerned registration dossier is therefore strongly recommended. FR-MSCA considers that a compliance check (CCH) would be the adequate regulatory tool (rather than substance evaluation) to address the inconsistencies or missing information pointed above.

Jeans bleaching:

This scenario includes only one contributing scenario (PROC 7: industrial spraying). The registrant specifies the following OCs and RMMs:

- Concentration < 5% in the aqueous solution
- Duration > 4 hours (full work day)
- Local exhaust ventilation (LEV) with 95% efficiency
- Respiratory protective equipment (RPE) with 90% efficiency (assigned protection factor of 10)
- Gloves.

[5] www.ebrc.de/mease.html.

The estimated inhalation exposure for this task is below the OEL for manganese and inorganic compounds (including potassium permanganate) set at 0.2 mg/m^3 (inhalable fraction) by the SCOEL for systemic effects. Nevertheless, the FR-MSCA considers that additional contributing scenarios (mixing and loading of potassium permanganate and maintenance and cleaning) are missing and should be included in this exposure scenario to describe the use properly and demonstrate safe use. Update of the concerned registration dossier is therefore strongly recommended. FR-MSCA considers that a compliance check (CCH) would be the adequate regulatory tool (rather than substance evaluation) to address the missing scenarios pointed above.

In view of the corrosive properties of potassium permanganate, the risk related to local effects is considered as managed as long as adequate protective equipments are worn, as detailed in section 7.9.9.

7.12.1.2. Consumer

One initial concern which justified the inclusion of the substance in the CoRAP was related to consumers uses and exposure of susceptible populations.

As the consumer exposure scenario was not detailed at all (only a title and the indication that use was infrequent and involved low amount) and as no exposure estimation nor risk characterisation were provided in the CSR at the start of the Substance Evaluation process, FR-MSCA asked the registrant to provide more information. As a result, the Lead registrant and one of the co-registrants (registrant 2) deleted the consumer exposure scenario, and advised against these uses. However, the other active co-registrant still supports consumer uses in its registration dossier, but do not provide any use description nor assessment to demonstrate how safe use can be achieved. Update of the registration dossier is necessary to either provide an assessment or remove/advise against the use. If spontaneous update by the concerned registrant is not undertaken, compliance check (Article 41(c)) would be the adequate regulatory tool (rather than substance evaluation) to address such discrepancy.

7.12.2. Environment

Not assessed during the evaluation of the substance.

7.12.3. Combined exposure assessment

Not assessed during the evaluation of the substance.

7.13. Risk characterisation

Not assessed during the evaluation of the substance. See also section 7.9.9.

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7.15. Abbreviations

Environmental release categories (ERC):

- ERC 1: Manufacture of the substance
- ERC 2: Formulation into mixture
- ERC3: Formulation into solid matrix
- ERC 4: Use of non-reactive processing aid at industrial site (no inclusion into or onto article)
- ERC 6a: Use of intermediate

- ERC 6b: Use of reactive processing aid at industrial site (no inclusion into or onto article)
- ERC 6c: Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article)
- ERC 6d: Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article)
- ERC 7: Use of functional fluid at industrial site
- ERC 8a: Widespread use of non-reactive processing aid (no inclusion into or onto article, indoor)
- ERC 8b: Widespread use of reactive processing aid (no inclusion into or onto article, indoor)
- ERC 8c: Widespread use leading to inclusion into/onto article (indoor)
- ERC 8d: Widespread use of non-reactive processing aid (no inclusion into or onto article, outdoor)
- ERC 8f: Widespread use leading to inclusion into/onto article (outdoor)

Process categories (PROC):

- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions
- PROC 4: Chemical production where opportunity for exposure arises
- PROC 5: Mixing or blending in batch processes
- PROC 7: Industrial spraying
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
- PROC 11: Non industrial spraying
- PROC 13: Treatment of articles by dipping and pouring
- PROC 15: Use as laboratory reagent
- PROC 28: Manual maintenance (cleaning and repair) of machinery

Product categories (PC):

- PC 14: Metal surface treatment products
- PC 21: Laboratory chemicals
- PC 37: Water treatment chemicals

Sector of end-uses (SU):

- SU 1: Agriculture, forestry and fishing
- SU 2a: Mining (without offshore industries)
- SU 2b: Offshore industries
- SU 4: Manufacture of food products
- SU 5: Manufacture of textiles, leather, fur
- SU 6a: Manufacture of wood and wood products
- SU 6b: Manufacture of pulp, paper and paper products
- SU 7: Printing and reproduction of recorded media
- SU 8: Manufacture of bulk, large scale chemicals (including petroleum products)
- SU 9: Manufacture of fine chemicals
- SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys)
- SU 11: Manufacture of rubber products
- SU 12: Manufacture of plastics products, including compounding and conversion
- SU 13: Manufacture of other non-metallic mineral products, e.g. plasters, cement
- SU 14: Manufacture of basic metals, including alloys
- SU 15: Manufacture of fabricated metal products, except machinery and equipment
- SU 16: Manufacture of computer, electronic and optical products, electrical equipment
- SU 17: General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment
- SU 18: Manufacture of furniture
- SU 19: Building and construction work
- SU 20: Health services
- SU 23: Electricity, steam, gas water supply and sewage treatment
- SU 24: Scientific research and development

Others abbreviations:

AC	Article category
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health & Safety)
ATP	Adaptation to technical and scientific progress
BW	Body weight
CAS	Chemical abstracts service
CCH	Compliance check
CLH	Harmonized classification
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CoRAP	Community Rolling Action Plan
CSR	Chemical safety report
DMEL	Derived minimal effect level
DNEL	Derived no effect level
DU	Downstream users
ECHA	European Chemicals Agency
ED	Endocrine disrupting
eMSCA	Evaluating Member State Competent Authority
ERC	Environmental release category
FR	France
IUCLID	International Uniform Chemical Information Database
LD50	Median lethal dose. The dose causing 50 % lethality
MMAD	Mass median aerodynamic diameter
MS	Member State
MSC	Member State Committee
MSCA	Member State Competent Authority
NCE	Normochromatic erythrocytes
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Level
PCE	Polychromatic erythrocytes
PBT	Persistent, Bioaccumulative, Toxic
PC	Product Category
PNEC	Predictive No Effect Concentration
PROC	Process category
PPE	Personal Protective Equipment
QSAR	Quantitative structure–activity relationship
RAC	Risk Assessment Committee
RMM	Risk management measures
RMOA	Risk Management Option Analysis
RPE	Respiratory protective equipment
SCOEL	Scientific Committee on Occupational Exposure Limits
SDS	Safety Data Sheet
SIEF	Substance Information Exchange Forum
STOT SE	Specific target organ toxicity after single exposure
SU	Sector of end-use
SVHC	Substance of very high concern

vPvB Very Persistent and very Bioaccumulative

The Appendix with confidential information has been removed from the public version of this document.