Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

potassium permanganate

EC Number: 231-760-3
CAS Number: 7722-64-7

CLH-O-0000001412-86-134/F

Adopted
9 December 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON POTASSIUM PERMANGANATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: potassium permanganate
EC number: 231-760-3
CAS number: 7722-64-7
Dossier submitter: ANSES, France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
24.03.2016	Germany		MemberState	1
Comment received				
Overall, the German CA supports the proposal for harmonised classification of potassium permanganate as Repr. 1B (H360Df). There is clear evidence of developmental toxicity and some evidence of effects on fertility in rats. According to Annex I: 3.7.2.4.2 of the CLP-Regulation the developmental effects which occur in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated that the developmental effects are secondary to maternal toxicity. However it should be described more in detail, why the effects found in the studies of Plodíkóva 2008 and 2009, like decrease of the fertility index, post-implantation loss and the resorptions, are not based on parental or maternal toxicity. The large reduction of body weight in males of almost 20 % in the highest dose group (Plodíkóva, 2008) and of the dams in the highest dose group (Plodíkóva, 2009) could have a significant impact on the fertility in the first study and on implantations and resorptions in the second study. In addition, the animals from the middle and the highest dose group in the second study (Plodíkóva, 2009) showed a strongly impaired health condition. If the described effects were caused by parental or maternal toxicity it would be necessary to value these effects differently. Please note that use of potassium permanganate also includes the disinfection of vegetables in some developing countries. Further comments concerning substance identity: - In IUCLID section 1.1 in the field "Type of substance" the origin of the substance is missing. Please add the missing information. - The reference substance dataset for potassium permanganate in IUCLID section 1.1 respectively IUCLID section 1.2 does not include the IUPAC name of the substance.				

Furthermore, no structural formula, SMILES notation or InChI code is given in reference substance dataset. Please add the missing information.
- The reference substance datasets for most of the impurities listed in IUCLID section 1.2 do not include a structural formula, SMILES notation or InChI code as well. Please add the missing information.
- In IUCLID section 1.2 eighteen impurities are given. Although seven of them are flagged as CBI in the IUCLID dossier, sixteen impurities are listed in part B, section 1.2, table 7 of the CLH report.
- In IUCLID section 1.2 eighteen impurities are given. For most of these impurities the given information are inconsistent respectively wrong. For example the impurity iron(2+) (=stated IUPAC name) is given together with the EC and CAS number for iron. Since iron(2+) respectively iron salts cannot be identified using the EC and CAS number for iron, the given identifiers should be deleted. Please check and revise the reference substance datasets for the impurities in IUCLID section 1.2 accordingly. The same applies to the confidential annex of the CLH report. In this document not only the wrong identifiers should be deleted, but the accompanying (wrong) harmonised classification for some of the impurities as well (e.g. see confidential annex of the CLH report, composition 2, impurity 1 and 2).
The latter aspect also applies to the (wrong) impurities and their harmonised classifications given in part B, section 1.2 of the public CLH report (e.g. "sodium" is given as impurity together with its current Annex VI entry: Waterreact. 1, H260; Skin Corr. 1B, H314).
Please revise the documents accordingly.
- In IUCLID section 1.2 and in the confidential annex of the CLH report (composition 4) one substance is listed under "Additives". According to the information given in the IUCLID file the function of the substance is not to stabilize the potassium permanganate. Since, only stabilising agents are additives in terms of REACH, the given substance cannot be listed under additives. (See also "Guidance for identification and naming of substances under REACH and CLP", section 2.2, table 2.2 "Definitions": "Additive: A substance that has been intentionally added to stabilise the substance 3. […] 3 In other areas an additive can also have other functions, e.g. pH-regulator or colouring agent. However, in the REACH regulation and in this TGD an additive is a stabilising agent.".) Please amend the IUCLID file and the confidential annex of the CLH report accordingly.
- Furthermore, it has to be mentioned that the IUPAC name stated in the reference substance data set for the substance listed as additive does not identify the same substance as the given CAS and EC number. Please replace the given IUPAC name.
- In IUCLID section 1.2 eighteen impurities are stated together with values for their typical concentration or their maximum concentration (as part of their concentration range). These values are partly not in accordance with the values given in the CLH report (part B, section 1.2, table 7) and in the four compositions tables given in the confidential annex of the CLH report. For example according to IUCLID section 1.2 the typical concentration of lead is ca. 0.002% w/w whereas in the CLH report the impurity lead is stated with a concentration range <0.001%. Please clarify these inconsistencies and amend the IUCLID file/report documents accordingly.
- In part B, section 1.2, table 7 of the CLH report "Chloride and chlorate" are given as impurities of potassium permanganate. No corresponding information are given in the IUCLID file (or in the confidential annex). There only chloride is identified as impurity. Please clarify this inconsistency.
- In the confidential annex of the CLH report in composition 4 the CAS No. identifying the third impurity is wrong. Please correct the given CAS No.

Dossier Submitter's Response

Classification proposal:
Thank you for your support.

Parental and maternal toxicity
In the one generation reproduction toxicity study (Plodíkóva, 2008), at the highest dose, a large reduction of body weight in males of almost 20 % was observed concomitently with decrease food consumption (17%). An increase incidence of stomach and duodenum irritations were also observed. In females, no effects on body weight were observed whereas decreased in food consumption (23%) from mating to lactation and stomach irritation were observed at the high dose level. Furthermore, based on the 28-day study in rats (2006), it cannot be excluded that at this dose level some haematological or biochemistral changes occurred. In this study, no parental toxicity was observed at the mid and low dose level.

In the developmental toxicity study (Plodíkóva, 2009), body weight loss was only observed in dams in the first days of treatment and decrease food consumption was observed until gestation day 14 at the highest dose group . In this group, corrected bw gain of dams (corrected for uterus weight) was only slightly lower than the control at necropsy (4%). Statistical difference was not recorded.

As conclude in the CLH report, spermiogenesis effects in male may be partly secondary to the general toxicity. The dose-related decreased in the fertility index may also have been partly link to the decrease food consumption in females. Overall, it is considered that category 2 is appropriate for fertility.

In the one-generation study, developmental effects observed in pups at all dose tested ie also at doses where no materno-toxicity is observed (a marked vacuolization of cell nuclei in cortex and/or hippocampus) is not considered secondary to parental toxicity. The increased in brain weight is not a typical secondary effect to materno-toxicity. However, it is only observed at the highest dose .

In the developmental toxicity study, it is not reported wether postimplantation losses observed at the highest dose were due to early or late resorptions. Furthermore, some developmental effects (delayed development) occurred at mid dose where only sporadic maternal toxicity occured and at 20 mg/kg bw without maternal toxicity.

Overall, although some maternal toxicity occurred at the high dose level in both studies, observed developmental effects (brain, total resorptions, increase in postimplantation losses, delayed development) were not considered secondary to parental or maternal toxicity and Repr. Cat. 1 B is considered warranted.

Uses
Noted. For information, potassium permanganate has not been approved in UE under pesticide regulation No 1107/2008 (2008/768 legislation).

Substance identity
At the stage of the assessment the IUCLID file and the CLH report will not be amended. However,
- we agree that the origin of the substance is missing in section 1.1.
- regarding the reference substance datasets, the reference substances were already in the IUCLID database, only a link has been made in the IUCLID file of potassium permanganate and we have not amended the reference substance dataset.

- The information about the impurities come from different sources: the registration dossiers of potassium permanganate which are confidential data and from literature data which are not confidential.

The data reported in IUCLID is a compilation of all the data found (registration dossiers and literature)
The data reported in the non confidential CLH report are only the non confidential data found in literature.
The data reported in the confidential annex of the CLH report are the data from the registration dossiers which are confidential.
Impurities which have been flag as confidential in the IUCLID file are the impurities where the maximal limit come from the registration dossiers which are confidential data.
The reason for explaining the difference of concentrations reported in IUCLID and in the CLH is the same as above: the concentrations reported in the non confidential CLH report are only the non confidential data found in literature (which are only maximum concentration). The concentrations reported in IUCLID are a compilation of all the data found and the concentrations reported in the confidential annex of the CLH report are the data from the registration dossiers which are confidential (there were typical and/or range values).

- Moreover about the impurities specified in section 1.2 in IUCLID, the information provided in the registration dossiers and found in literature don't specify the form of the impurities, only the element has been taken into account and the harmonised classification related to the element has been indicated.
For iron, indeed the IUPAC name (iron (+2)) in the reference substance dataset is incorrect however the information will not been amended and is the same as provided in the registration dossiers.
About the additive in composition 4, it is specified as additive in the registration dossier.
For the inconsistency between "chloride and chlorate" and only "chloride", IUCLID is not adapted to inorganic substance.

RAC's response

Effects on fertility and sexual function: In the one-generation study in rats a decrease in the fertility index, in dams bearing live pups, as well as the number of born pups were reported in the highest dose group. However, at this dose level severe systemic toxicity was observed in males, including body weight loss, dyspnea, decreased activity, red secretion around nose or eyes, rigidity, piloerection and salivation. Macroscopic and microscopic examination also showed marked changes in the stomach, such as ulceration, erosion and inflammation. In pregnant dams effects including erosions, ulceration and haemorrhage were reported on the digestive tract, but there was no apparent correlation between the stomach effects in females and the ability to achieve pregnancy.
A reduction in the number of implantations and viable fetuses has also been reported in a study where female mice were exposed to manganese chloride, and a reduction in number of pregnant females were reported in rats following exposure to Mn_3O_4. However, due to the highly corrosive/oxidizing effect of potassium permanganate, it is not possible to draw conclusions from these studies, as the effects seen with potassium permanganate were seen at the high dose which caused severe toxicity.

In males effects on spermatogenesis were reported in the presence of a decreased body weight and severe irritation of the digestive tract in the high dose group. The effects reported on the testes could have influenced the decreased fertility index. However, the data available does not permit to identify which females were mated with which male, therefore a clear link could not be established. Male mice exposed to other manganese compounds haves also shown effects on male reproductive organs, sperm quality and fertility. Further, in male rats a Mn related maturational delay in male reproductive parameters was reported following exposure to Mn_3O_4 at day 100 of exposure. However, from the one-generation study with potassium permanganate it is not clear if the effects

on male reproductive organs is responsible for the effects on fertility reported since severe toxicity in males was reported at the same dose levels as testicular toxicity was observed. In the 28-day oral and dermal repeated dose toxicity studies no clear relationship between exposure to potassium permanganate and effects on male and female reproductive organs could be seen. RAC therefore concludes that the effects reported in the one-generation study observed in the high dose group in the presence of severe toxicity are considered to be secondary non-specific concequences of parental toxicity. Also taking into account the general bad quality of the study (very limited statistical analysis, no historical control data) RAC concludes that classification of potassium permanganate as Repr. 2 is not justified for fertility and sexual function.

Developmental toxicity: In the one-generation study a decrease in gestation index and a slight decrease in viability index was reported in the high dose (320 mg/kg bw/d). However, as regards the effect reported on gestation index, it is not clear from the data reported if this is related to an effect on fertility or development. In pups it was evident that the main target organ was the brain with increased weight in the high dose and marked vacuolisation of cell nuclei (indicating degenerative processes) in the cortex and/or hippocampus in all treated groups with increased severy with increasing dose. Maternal toxicity included severe microscopic changes in the stomach in the high dose group, however, in the lower dose-groups without severe maternal toxicity marked vacuolisation of cell nuclei was reported. Other studies have also reported that exposure to other manganese compounds can induce neurotoxicity and produce central nervous system damage.

In the developmental toxicity study a three times increase in post-implantation losses and an increase in total resorptions were reported compared to control animals in the high dose group (500 mg/kg bw/d). The maternal toxicity included a statistically significant decrease in body weight, with only a marginal decrease in corrected body weight gain. However, several clinical signs and severe microscopic changes in the stomach in the high dose group was reported therefore RAC put less weight on the results form this study. RAC therefore concludes that the effects reported in the one-generations toxicity study on the histopathological changes in pup brain at doses not causing maternal toxicity is considered as evidence of developmental toxicity. However, due to the limitations of the study (lack of statistical analysis, no historical control) and no available developmental neurotoxicology study following exposure to potassium permanganate, a classification in Repr. 2 is considered justified.

As regards the uses and substance ID, RAC has no further comments.

Date	Country	Organisation	Type of Organisation	Comment number
29.03.2016	Netherlands		MemberState	2
Comment received				
No information is provided regarding the toxicokinetic properties of KMnO4. However, given the strong oxidising potential it can be expected that a reduced form of Mn will form in the stomach. Further information on the reduced form available for systemic exposure may allow read-across from other tested Mn oxidation forms. Please explain the effect scoring system (example [0-0-0-1]) used in the summary for repeated dose toxicity. No information on the statistical significance of several reproductive effects is present in the proposal and probably the original report. Is it possible to calculate the statistical significance based on the available data?				

Dossier Submitter's Response

Read-across for other Mn oxidation forms:

There are several existing reviews on manganese toxicity (e.g. EHC, 1981; IPCS, 1999; SCOEL, 2011; WHO, 2011; ATSDR, 2012; MAK, 2012). However, as the registration dossier contains good quality data showing effects, we have not reviewed the entire database in our CLH dossier. It should be noted that our RCOM are based on these studies from the registration dossier together with previous international assesments.

Manganese inorganic compounds include soluble and insoluble compounds such as: manganese, manganese chloride, manganese sulfate, manganese (III)oxide, manganese dioxide.

Considerable information are available with soluble manganese chloride and sulfate as they were more bioavailable than other insoluble compounds.

Toxicokinetics:

The permanganate ion is the best known form of Mn^{VII}. Permanganate, which is a good oxidant in basic solutions, is reduced to Mn2+ in acid solutions. Limited data suggest that manganese can undergo changes in oxidation state within the body. The rate and extent of manganese reduction/oxidation reactions might be important determinants of manganese retention in the body (IPCS, 1999).

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 children than in adults, it is not effectively eliminated from the body and even less effectively from the brain (MAK, 2012)

Comparative toxicology

Potassium permanganate differs from other manganese compounds because it is an oxidant that can cause corrosion to skin. Other inorganic manganese compounds have very low acute toxicity. Therefore, potassium permanganate local effects is expected to be higher than other compounds. Nevertheless, systemic toxicity data on other soluble manganese inorganic compounds may support the classification proposal (see below).

Data on other Manganese inorganic compounds

The central nervous system is the main target of manganese toxicity.

In human, there are no available studies evaluating the reproductive effects in humans following oral manganese exposure. However, "human data support the hypothesis that oral exposure to elevated manganese may be detrimental to neurodevelopment" (ATSDR, 2012). In the review of IPCS, 1999, it is concluded that reproductive effects of chronic inhalation exposure to manganese include decreased libido, impotence, and decreased fertility in men; information is not available on reproductive effects in women.

In animals, as highlight by the lead registrant, no effects on reproductive organs were observed in a 14-d study in rats and 2-year studies in rats and mice (NTP 1993). SCOEL 2011 concluded that "there is little evidence for reproductive or developmental toxicity". However, in the review of IPCS, 1999, it is concluded that manganese can cause direct damage to the testes.

Furthermore, although results from the numerous animal studies were inconsistent, "the weight of evidence suggests that excess in manganese exposure during development can

lead to alterations in brain chemistry and behavioral development" (ATSDR, 2012). IPCS, 1999 also reviewed some studies showing late resorptions.

Overall data on other manganese compounds support the need of a classification for reproductive and developmental toxicity.

Scoring system:
[0-0-0-1] used in the summary for repeated dose toxicity means that the incidence of animals with an observed toxicological finding was: 0 in control, 0 at 40 mg/kg bw, 0 at 100 mg/kg bw and 1 at 250 mg/kg bw per day.

Statistical significance:
We agree that no information on the statistical significance of several reproductive effects is available. We do not have the possibility to calculate it and this is considered a weakness of the study.

References:
ATSDR (2012) Agency for Toxic Substances and Disease Registry Toxicological Profile for Manganese

EHC (1981), WHO Environment Health criteria 17, Manganese

German MAK commission (2012) Manganese and its inorganic compounds

IPCS (1999) Manganese and its compounds. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 12).

SCOEL (2011) Recommendation from the Scientific Committee on Occupational Exposure Limits for manganese and inorganic manganese compounds

WHO, Background document for development of WHO guidelines for drinking-water quality. (2011) Manganese in drinking-water. WHO/SDE/WSH/03.04/104/Rev/1

RAC's response

RAC aknowledges the information regarding the toxicokinetics of potassium permanganate, the comparative toxicology and the data on other manganese compounds provided by the DS. Information regarding effects on fertility and development has been included in the RAC Opinion. RAC also considers that information on the statistically significance of the effects would have been helpful.

Date	Country	Organisation	Type of Organisation	Comment number
04.04.2016	Spain	Carus Europe S.L.	Company-Manufacturer	3

Comment received

This submission is made by Carus Europe S.L. in its capacity as Lead Registrant for the substance potassium permanganate (KMnO4).

KMnO4 is an inorganic manganese compound. Manganese (Mn) is a naturally occurring and abundant element. It is essential in biological systems but deficiency or excess of this mineral can lead to adverse effects. Like the majority of trace elements and vitamins, it exhibits a U form toxic curve. Potassium permanganate is a strong oxidant used primarily in industrial setting for water purification.

Summary

There are many studies publicly available on Manganese (including inorganic compounds) which have not been assessed by the Rapporteur and which show no reproductive toxicity effects.

There are only two studies used by the Rapporteur to support the proposal for reproductive toxicity classification, (i) a pre-natal developmental toxicity and (ii) a one-generation study. However, both studies were conducted at very high doses and lack some relevant parameters thereby questioning their reliability.

Additional studies should be included in the review and are presented in the CLH Document.

From a thorough analysis of a larger pool of studies, the toxicokinetic behavior of the substance and its degradation products it may be concluded that effects on fertility occurred at high doses and as secondary effects to general toxicity leading to a STOT RE2 self- classification.

Therefore, as a precautionary approach the Lead Registrant proposes a STOT RE2 self-classification together with a harmonized CLP classification of KMnO4 as reproductive toxicity Cat 2 and developmental toxicity Cat 2 as there is some evidence of developmental toxicity although not conclusive. This is envisaged as an extremely precautionary approach.

ECHA note: An attachment was submitted with the comment above. As it contains the same content as the comment, it is not provided as a separate attachment.

The following attachment was submitted with the comment above: CLH_RESP_CARUS_KMnO

Dossier Submitter's Response

STOT RE self-classification

Based on the 28-day toxicity study, STOT RE 2 self-classification on liver is proposed. No liver toxicity (pathology, weight) were observed in the one-generation or developmental toxicity study performed with potassium permanganate. Nevertheless, we agree that at 350 mg/kg bw in the one-generation study and at 500 mg/kg bw in the developmental toxicity study, some sporadic haematological and biochemical findings may occur as was observed in the 28-day study.

Toxicokinetics data

Thank you for the review on the toxicokinetic of potassium permanganate. We agree that data on other inorganic compounds support the need of a classification for reproductive and developmental toxicity of potassium permanganate.

Other data on Mn compounds

In animals, as highlight by the lead registrant, no effects on reproductive organs were observed in a 14-d study in rats and 2-year studies in rats and mice (NTP 1993). SCOEL 2011 concluded that "there is little evidence for reproductive or developmental toxicity". We agree that no effets on reproductive organs were observed in available studies with other inorganic manganese compounds. Furthermore, although results from the numerous animal studies were inconsistent, "the weight of evidence suggests that excess in manganese exposure during development can lead to alterations in brain chemistry and

behavioral development" (ATSDR, 2012). IPCS, 1999 also reviewed some studies showing late resorptions.

Conclusion
Overall, new data provided by the lead registrant do not change the classification proposal for potassium permanganate as H360Df.

RAC's response

RAC agrees that some information regarding the toxicokincetic in the CLH report would have been helpful. Since no assessment of a STOT RE classification was included by the DS, a possible STOT RE classification for potassium permanganate has not been assessed by RAC. Information regarding effects on fertility and development following other manganese compounds has been included in the RAC opinion. As regards the final classification agreed by RAC on the effects on fertility and development following exposure to potassium permanganate, please see response to comment number 1.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
29.03.2016	Netherlands		MemberState	4

Comment received

We agree with the need for a classification for reproductive toxicity.
A classification for reproductive toxicity Cat 1B is proposed for the developmental endpoint based on the low gestation index (64%) and the high rate of post-implantation losses (42%). Although these effects were only noted at the high doses (320 mg/kg bw/day in the one-gen study and 500 mg/kg bw/day in the pre-natal study) in the presence of maternal toxicity, we agree that this is relevant for classification as no excessive maternal toxicity (CLP 3.7.2.4.4) was observed. However, it is unclear from the comparison with the criteria why the observed low gestation index and increase in post-implantation loss at maternally toxic dose levels is considered not secondary to the maternal toxicity (decreased body weight, dyspnea / reduced body weight, clinical effects, decreased uterus weight, stomach effects). We do not agree with the argument that the absence of excessive parental toxicity justifies that the developmental effects are not secondary to the maternal toxicity. This would require further justification including additional details on the study like the incidence of full resorption in all dose groups. In addition, the induction of comparable developmental effects by other corrosive substances could be checked to determine whether such developmental effects are always observed after induction of such gastric effects.
In addition, decreased pup body weights, skeletal abnormalities, late opening of the eye and histopathological effects on pup brain were observed at doses not resulting in maternal toxicity. However, the adversity of these effects does not normally warrant Cat 1B (3.7.2.3.3).

At page 24, the effects of the substance on the female reproductive system are described. Several effects are seen in the ovaries and in the uterus. However, these effects are not dose-related, and no statistical analysis was performed. How do these compare to historical controls? Adverse effects regarding testes and epididymis and fertility (number of pregant females) were only observed at high doses that also caused systemic toxicity in males in the 1-generation study, and therefore Cat. 2 is indeed appropriate. In addition, the statistical significance of these effects is unclear.

Dossier Submitter's Response

Thank you for your support on category 2 for fertility and adverse effects regarding testes and epididymis.

Additional details in the study
In the study, the number of females without foetuses but with implantation were dose-related and were: 3, 3, 4, 8 at 0, 20, 100 and 500 mg/kg bw per day, respectively.

No historical control data are available in the studies.

Corrosivity and developmental effects
Corrosivity will impact the general health status of parents. This local effects will be considered as a marker of maternal or parental toxicity in a weight-of-evidence approach with other parameters (mainly body weight, food consumption, clinical signs). A detailed analysis on the impact of corrosivity on developmental effects has not be conducted nor found in the literature. The remaining question is if the substance can impact developing organism at doses that will not lead to major toxicity in parents. We believe that the data show an over-sensitivity of foetuses compared to parents whatever the mechanism involved.

RAC's response

As regards to the final classification agreed by RAC on the effects on fertility and development following exposure to potassium permanganate, please see response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
04.04.2016	Spain	Carus Europe S.L.	Company-Manufacturer	5

Comment received

KMnO4 is an inorganic manganese compound. Manganese (Mn) is a naturally occurring and abundant element. It is essential in biological systems but deficiency or excess of this mineral can lead to adverse effects. Like the majority of trace elements and vitamins, it exhibits a U form toxic curve. Potassium permanganate is a strong oxidant used primarily in industrial setting for water purification.

Summary

There are many studies publicly available on Manganese (including inorganic compounds) which have not been assessed by the Rapporteur and which show no reproductive toxicity effects.

There are only two studies used by the Rapporteur to support the proposal for reproductive toxicity classification, (i) a pre-natal developmental toxicity and (ii) a one-generation study. However, both studies were conducted at very high doses and lack some relevant parameters thereby questioning their reliability.

Additional studies should be included in the review and are presented in the CLH Document.

From a thorough analysis of a larger pool of studies, the toxicokinetic behavior of the substance and its degradation products it may be concluded that effects on fertility occurred at high doses and as secondary effects to general toxicity leading to a STOT RE2 self- classification.

Therefore, as a precautionary approach the Lead Registrant proposes a STOT RE2 self-classification together with a harmonized CLP classification of KMnO4 as reproductive toxicity Cat 2 and developmental toxicity Cat 2 as there is some evidence of

developmental toxicity although not conclusive. This is envisaged as an extremely precautionary approach. --- *ECHA note: An attachment was submitted with the comment above. As it contains the same content as the comment, it is not provided as a separate attachment.* *The following attachment was submitted with the comment above: CLH_RESP_CARUS_KMnO*
Dossier Submitter's Response
Please see response to comment number 1 and 3.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
04.04.2016	Belgium		MemberState	6
Comment received				
BE CA supports the proposal to classify Potassium permanganate as Repr. 1B. In Plodiková 2008, body weight of parental generation was only affected in males at the highest dose at the end of the exposure period and cannot explain the decreased of conception index (64% at the highest dose vs 84% in control group). Moreover, BE CA notes that the number of live born pups tend to decrease from the lowest dose (207, 164, 163, 99 at 0, 20, 80, 320 mg/kg bw/d respectively). In the observation of pups, examination of brain showed a significant increase in absolute and relative brain weight at the highest dose furthermore a marked vacuolization of cell nuclei in cortex and/or hippocampus was detected (0, 12, 15, 16 at 0, 20, 80, 320 mg/kg bw/d respectively). In plodiková 2009, body weight of dams was only significantly decreased between gestational day 8 and 17 and cannot explain some maternal effects such as the increase of resorptions (2.83 at the highest dose vs 0.61 in control group), the increase of post-implantation loss (14.18, 22.80, 24.65 and 45.25 at 0, 20, 100, 500 mg/kg bw/d respectively). Skeletal alteration was also increased with dose dependency (incomplete ossification of sternum and cervical vertebrae). Based on all these results, BE CA agrees with of H360D and suggests to modify the "f" in "F" (H360DF) considering important effects on the fertility parameters.				
Dossier Submitter's Response				
Thank you for your support for the classification proposal H360D. The fertility effects observed only at the highest dose is not considered sufficient to classify in category 1 because they appear at doses where toxicity is observed. Category 2 is therefore considered more appropriate for fertility effects.				
RAC's response				
Please see response to comment number 1.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
24.03.2016	Germany		MemberState	7
Comment received				
harmonised classification and labelling proposal M-factors (p. 4): This classification proposal deals not with environmental effects as there is the existing classification Aquatic Acute 1; H400 and Aquatic Chronic 1; H410. We would like to comment that there is no				

M-factor indicated, but we think that it is necessary. For Potassium Permanganate we would suggest 10 for both (acute and chronic).
Dossier Submitter's Response
Thank you for your comment. We note that M-factor may be necessary. Nevertheless, environmental effects were not adress in the report.
RAC's response
Noted.

CONFIDENTIAL ATTACHMENTS

1. *CLH_RESP_CARUS_KMnO*. Submitted on 04/04/2016 by Carus Europe S.L. [Please refer to comment No 3 and 5]