Committee for Risk Assessment

RAC

Annex 1

Background document

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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

9 December 2016

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Substance Name: Potassium Permanganate

EC Number: **231-760-3**

CAS Number: **7722-64-7**

Index Number: **025-002-00-9**

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Version number: 2 **Date:** November 2015

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	**Potassium Permanganate**
EC number:	**231-760-3**
CAS number:	**7722-64-7**
Annex VI Index number:	**025-002-00-9**
Degree of purity:	>= 97%
Impurities:	Sulphate, chloride, water insoluble matters

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Ox. Sol. 2 – H272 Acute Tox. 4* – H302 Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410
Current proposal for consideration by RAC	Repr. 1B – H360Df
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Ox. Sol. 2 – H272 Acute Tox. 4* – H302 Repr. 1B – H360Df Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410

***** the classification as obtained from Annex VII shall then substitute the minimum classification indicated in this Annex it is differs from it.

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				Not evaluated
2.2.	Flammable gases				Not evaluated
2.3.	Flammable aerosols				Not evaluated
2.4.	Oxidising gases				Not evaluated
2.5.	Gases under pressure				Not evaluated
2.6.	Flammable liquids				Not evaluated
2.7.	Flammable solids				Not evaluated
2.8.	Self-reactive substances and mixtures				Not evaluated
2.9.	Pyrophoric liquids				Not evaluated
2.10.	Pyrophoric solids				Not evaluated
2.11.	Self-heating substances and mixtures				Not evaluated
2.12.	Substances and mixtures which in contact with water emit flammable gases				Not evaluated
2.13.	Oxidising liquids				Not re-evaluated
2.14.	Oxidising solids			Ox. Sol. 2 – H272	Not re-evaluated
2.15.	Organic peroxides				Not evaluated
2.16.	Substance and mixtures corrosive to metals				Not evaluated
3.1.	Acute toxicity - oral			Acute Tox. 4* – H302	Not re-evaluated
	Acute toxicity - dermal			None	Not evaluated
	Acute toxicity - inhalation			None	Not evaluated
3.2.	Skin corrosion / irritation			None	Not evaluated
3.3.	Serious eye damage / eye irritation			None	Not evaluated
3.4.	Respiratory sensitisation			None	Not evaluated
3.4.	Skin sensitisation			None	Not evaluated
3.5.	Germ cell mutagenicity			None	Not evaluated
3.6.	Carcinogenicity			None	Not evaluated
3.7.	Reproductive toxicity	**Repr. 1B – H360Df**	**None**	**None**	Based on available studies
3.8.	Specific target organ toxicity –single exposure			None	Not evaluated
3.9.	Specific target organ toxicity – repeated exposure			None	Not evaluated
3.10.	Aspiration hazard			None	Not evaluated

4.1.	Hazardous to the aquatic environment			Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410	Not evaluated
5.1.	Hazardous to the ozone layer			None	Not evaluated

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Danger

Hazard statements: H360Df

GHS Pictogram: 

Proposed notes assigned to an entry: none

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

The harmonised classification of potassium permanganate has been inserted in the table 3.1 of the CLP regulation (1272/2008). No discussion of potassium permanganate classification occurred since then to our knowledge.

2.2 Short summary of the scientific justification for the CLH proposal

This proposal is based on the information as available on two study reports submitted by the registrant.

When administered to rats, potassium permanganate induced effects on sexual organs and function. In a one generation toxicity study, potassium permanganate induced a significant decreased weight of prostate gland and various damages of spermatogenesis. These effects occurred at a dose associated with decreased body weight and irritation of digestive tract. Decrease of fertility index was also recorded, showing a decreased ability of the animals to achieve a pregnancy. It can be hypothesized that the decreased number of pregnant females is related to the effects on spermatogenesis. However, considering that only slight or moderate damage of spermiogenesis was observed, it is not clear if the effects on testes were sufficient to explain the decrease of fertility. Therefore, it cannot be excluded that the decreased fertility index was, at least partially, female dependent. Considering the low systemic effects noted in females, the decreased number of pregnant females cannot be considered a secondary non-specific consequence of general toxicity.

Since the adverse effects are slight to moderate damages of spermiogenesis and because decreased fertility index were only observed at a high dose causing systemic toxicity, the evidence is not sufficiently convincing to place the substance in Category 1 for fertility endpoint. However, a classification for reproductive toxicity category 2 is judged appropriate.

When administered to rats, potassium permanganate induced effects on development. In a one generation study, decreased gestation index was observed. This is consistent with the increase of post-implantation loss and resorption reported in a prenatal toxicity study. Other developmental effect observed in the one generation study included vacuolisation of cell nuclei in cortex and/or in hippocampus and a late opening of eyes.

In the prenatal developmental toxicity study, decreased pup body weights and skeletal abnormalities (mainly decreased number of ossification sites in sternum and incomplete ossification of cervical vertebrae) were also observed.

A classification for reproductive toxicity category 1B is thus proposed for developmental endpoint based on the low gestation index and high rate of post-implantation losses. Indeed, since the effects are severe and not considered as a non-specific consequence of maternal toxicity, the evidence is sufficient enough to not propose a Category 2. Other developmental effects of lower severity (late opening of eye, skeletal variation and histopathological effects on pup brain) were also reported and occurred at doses not associated with maternal toxicity and were not related to a decreased pup body weight.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

The classification of potassium permanganate is harmonised in Annex VI of CLP under the index number 025-002-00-9 as follows:

Classification according to Regulation (EC) No 1272/2008 (CLP)		
Class of danger	Ox. Sol. 2	
	Acute Tox. 4*	
	Aquatic Acute 1	
	Aquatic Chronic 1	
Hazard Statement	H272	May intensify fire; oxidiser
	H302	Harmful if swallowed.
	H400	Very toxic to aquatic life
	H410	Very toxic to aquatic life with long lasting effects

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

The notified classifications are summarized below. The notified classifications (184 notifiers) corresponding to the harmonized classification were not reported in the table.

Hazard class and category code(s)	Hazard statement code(s)	Number of notifiers
Ox. Sol. 2 Acute Tox. 4 Aquatic Chronic 1	H272 H302 H410	34
Not classified		30
Ox. Sol. 2 Acute Tox. 4 Skin Corr. 1B Aquatic Acute 1 Aquatic Chronic 1	H272 H302 H314 H400 H410	23
Ox. Sol. 2 Acute Tox. 4 Skin Corr. 1C Aquatic Acute 1 Aquatic Chronic 1	H272 H302 H314 H400 H410	23
Skin Irrit. 2 Eye Irrit. 2 STOT SE 3 Muta 2 Carc 1B	H315 H319 H336 H341 H350	10

Aquatic Chronic 3	H412	
Ox. Sol. 2 Acute Tox. 4 Skin Corr. 1C Aquatic Acute 1 Aquatic Chronic 1	H272 H302 H314 H400 H410 H373	5
Ox. Sol. 2 Acute Tox. 4 Skin Corr. 1C Aquatic Acute 1 Aquatic Chronic 1	H272 H302 H314 H400 H410	5
Ox. Sol. 2 Acute Tox. 4 Skin Corr. 1C Aquatic Acute 1 Aquatic Chronic 1	H272 H302 H314 H400 H410	3
Ox. Sol. 2 Acute Tox. 4 Aquatic Chronic 1	H272 H302 H410	3
Ox. Liq. 1 Acute Tox. 4 Skin Corr. 1A Acute Tox. 4	H272 H302* H314 H332	1
Aquatic Chronic 3	H412	1
Ox. Sol. 2 Acute Tox. 4 Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H272 H302 H319 H400 H410	1

*Skin Corr. 1B: 50% ≤ C < 70%
Ox. Liq. 1: 70% ≤ C ≤ 100%
STOT SE 3: 35% ≤ C ≤ 100%
Skin Irrit. 2: 35% ≤ C < 50%
Skin Corr. 1A: 70% ≤ C ≤ 100%
Ox. Liq. 2: 50% ≤ C < 70%
Eye Dam. 1: 8% ≤ C < 50%
Eye Irrit. 2: 5% ≤ C < 8%

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Available data show that potassium permanganate has a CMR property, i.e. reproductive toxicity that is not currently harmonised and justify a harmonised classification and labelling according to article 36 of CLP.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

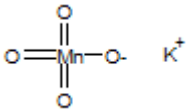
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	231-760-3
EC name:	Potassium permanganate
CAS number (EC inventory):	7722-64-7
CAS number:	7722-64-7
CAS name:	Permanganic acid (HMnO4), potassium salt (1:1)
IUPAC name:	Potassium oxido(trioxo)manganese
CLP Annex VI Index number:	025-002-00-9
Molecular formula:	HMnO4.K / KMnO4
Molecular weight range:	158.03g/mol

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Potassium permanganate	> 99%	> 97%	

Current Annex VI entry: H272, H302*, H400, H410

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Water insoluble matter		< 0.2%	
Sulphate		< 0.05%	
Sodium		< 0.02%	
Calcium		< 0.015%	
Magnesium		< 0.01%	
Chloride and chlorate		< 0.01%	
Iron		< 0.005%	
Total nitrogen		< 0.003%	
Lead		< 0.001%	
Chromium		< 0.001%	
Nickel		< 0.001%	
Zinc		< 0.001%	
Cadmium		< 0.0005%	
Cobalt		< 0.0005%	
Copper		< 0.0005%	
Arsenic		< 0.0001%	

Current Annex VI entries:

Sodium: Water-react. 1, H260; Skin Corr. 1B, H314

Calcium: Water-react. 2, H261

Magnesium: Pyr. Sol. 1, H250; Water-react. 1, H260

Nickel: Skin Sens. 1, H317; Carc. 2, H35 ; STOT RE 1, H372**; Aquatic Chronic 3, H412

Zinc: Pyr. Sol. 1, H250; Water-react. 1, H260; Aquatic Acute 1, H400; Aquatic Chronic 1, H410

Cadmium: Pyr. Sol. 1, H250; Acute Tox. 2, H330; Muta. 2, H341; Carc. 1B, H350; Repr. 2, H361fd; STOT RE 1, H372**; Aquatic Acute 1, H400; Aquatic Chronic 1, H410

Cobalt: Skin Sens. 1, H317; Resp. Sens. 1, H334; Aquatic Chronic 4, H413

Arsenic : Acute Tox. 3*, H301; Acute Tox. 3*, H331; Aquatic Acute 1, H400; Aquatic Chronic 1, H410

1.2.1 Composition of test material

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance at 20°C and 101,3 kPa	Dark purple or bronze-like, odourless crystals ; Almost opaque by transmitted light and of a blue metallic luster by reflected air Sweet with astringent after-taste Purple orthorhombic crystals	Merck Index 14th Ed (2006) CRC Handbook 86th Ed (2005-2006)	Handbook data
Melting/freezing point	Decomposition at 240°C Decomposition	Merck Index 14th ed (2006) CRC Handbook 86th Ed (2005-2006)	Handbook data
Boiling point	No need to be conducted as decomposition occurs before boiling	-	
Relative density	2.7 at 20°C	Merck Index 14th ed (2006) CRC Handbook 86th Ed (2005-2006)	Handbook data
Vapour pressure	Potassium permanganate is an inorganic salt and as such has negligible volatility at environmentally relevant temperatures.	-	
Surface tension	Surface tension is not applicable to inorganic salts	-	
Water solubility	7.60g/100g = 76g/L at 25°C	CRC Handbook 86th Ed (2005-2006)	Handbook data
Partition coefficient n-octanol/water	No need to be conducted as the substance is an inorganic salt	-	
Flash point	Not applicable because it is a solid	-	

Flammability	Not combustible but enhances combustion of other substances. Gives off irritating or toxic fumes (or gases) in a fire If the combustible material is finely divided the mixture may be explosive Contact with liquid combustible materials may result in spontaneous ignition	HSDB – Toxnet: Association of American Railroads Emergency handling of hazardous materials in surface transportation ; 1994, p903	
Explosive properties	No chemical group associated with explosive properties Risk of fire and explosion on contact with combustible substances or reducing agents.	HSDB – Toxnet: Association of American Railroads Emergency handling of hazardous materials in surface transportation ; 1994, p903	
Self-ignition temperature	Not combustible but enhances combustion of other substances. Gives off irritating or toxic fumes (or gases) in a fire If the combustible material is finely divided the mixture may be explosive Contact with liquid combustible materials may result in spontaneous ignition	HSDB – Toxnet: Association of American Railroads Emergency handling of hazardous materials in surface transportation ; 1994, p903	
Oxidising properties	Strong oxidising agent Classification Ox Sol 2 - H272		
Granulometry	Mass median : 175.8 µm Particle size: D90 < 298 µm, D10 < 106.1 µm	CSR of potassium permanganate (no study report provided)	Measured, laser diffraction method
Stability in organic solvents and identity of relevant degradation products	No need to be conducted as the substance is an inorganic salt Reacts with ethanol	- CRC Handbook 86th Ed (2005-2006)	 Handbook data

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.	-	
Viscosity	Not applicable because it is a solid	-	

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for this dossier.

2.2 Identified uses

Potassium permanganate is a highly oxidative agent. Its primary uses consist in control of odour and taste, remove colour, control biological growth and remove iron and manganese (EPA, 1999). According to the registration dossier, potassium permanganate is used by industrials, professionals and consumers as a laboratory and water treatment chemical in various sectors of end use (such as, agriculture, forestry and fishing (SU 1); mining (SU 2a) manufacture of various products (SU 4, 6, 8, 9, 12, 15, 16, 18); formulation of preparation (SU 10); electricity, steam, gas water supply and sewage treatment (SU 23); scientific research and development (SU 24).

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not evaluated in this dossier.

4.2 Acute toxicity

Not evaluated in this dossier.

4.3 Specific target organ toxicity – single exposure (STOT SE)

Not evaluated in this dossier.

4.4 Irritation

Not evaluated in this dossier.

4.5 Corrosivity

Not evaluated in this dossier.

4.6 Sensitisation

Not evaluated in this dossier.

4.7 Repeated dose toxicity

The following summaries were issued from the registration dossier available in the ECHA website (2014). Considering the level of details, the reported results cannot be adequately assessed.

In a study by oral route, Wistar rats (males/females) were exposed to 40, 100 and 250 mg/kg bw/day for 28 days. Two satellites groups exposed to vehicle or to 258 mg/kg bw/day for 28 days with a recovery period of 14 days were also included.

There was no mortality in this study. There was a slight decreased body weight at all doses in males and at the highest dose in females. Decreased body weight gain was also reported at all doses in males and at the two highest doses in females. These effects were associated with a reduction of food consumption. Decreased body weight and body weight gain were reversible during the recovery period, except body weight in males that was still lower than that of control at the end of application. The water consumption was decreased at 250 mg/kg bw/day in males and females. Variations in haematology (increased leukocytes, decreased lymphocytes, increased PT, total erythrocyte count, haematocrite and haemoglobin), biochemistry (decreased total protein, albumin and cholesterol, increased ALP, creatinine and calcium) and urinalysis (decrease of urine volume, increase of pH, specific weight and content of protein) were reported, some from 100 mg/kg bw/day. Decreased absolute weight of liver was found at the highest dose but the relative weight was increased at all doses in males. Increased weight of spleen (absolute and relative) was reported in males and females at 250 mg/kg bw/day. In females, kidney weights (relative and absolute) were also increased at this dose. At microscopy, the affections were often diagnosed in the liver and stomach in both sexes. In females, eosinophil infiltration and oedema of mucosa were found in the stomach of 6 females at the highest dose. Similar effects were not reported in other groups. Only sporadic changes were reported in the liver or stomach of males. Areactive necrosis of the mucosa of rectum was observed of males (0-0-0-3). Very few histopathological findings were recorded in brain (focal proliferation of glial cells in one male and one female, proliferation of ependymal cells in one female and oedema in one female, all at 250 mg/kg bw/day).

Concerning reproductive organs weight, an increased relative weight of testes and epididymides were recorded at 100 and 250 mg/kg bw/day. Absolute weight of testes was slightly increased in all treated groups. Slight increased absolute weight of epididymides was found at 100 and 250 mg/kg bw/day. These effects were not found in the satellite groups. In females, increase of absolute and relative weight of uterus was found in all treated groups, including the satellite treated group. Histopathological effects in the male reproductive tract were sporadic: atrophy of germinal epithelium of testes (1-0-0-0), inflammation of epididymis (1-0-0-0) and focal interstitial inflammation of the prostate (3-0-0-0). Lactating mammary gland were found in 3-2-1-0 males and involution of the mammary gland in 0-2-0-0 males. In the satellite groups, focal interstitial inflammation in prostate gland (4-1 males), proliferation of epithelium in prostate gland (1-0 males) and lactating mammary gland (2-0 males) were observed. In females, hydrometra of uterus (0-0-1-0) and involution of the mammary gland (5-5-3-3) were reported. In the satellite groups, hydrometra of uterus was diagnosed in 0-2 females, fibrosis of endometrium in uterus of 0-4 females and involution of mammary gland in 3-4 females.

In a study by dermal route, Wistar rats (males/females) were exposed to 150, 300 and 600 mg/kg bw/day for 28 days. Two satellites groups exposed to vehicle or to the highest dose of potassium permanganate for 28 days with a recovery period of 14 days were also included.

There was no mortality in this study. Slight decreased body weight and more marked decreased body weight gain were reported at all doses in both sexes. This was associated with no or low reduction of food consumption. Variations in haematology (increased monocytes, decreased lymphocytes), biochemistry (sodium ALT) and urinalysis (decreased urine volume, increased pH) were reported, with some at all tested doses. No statistically significant treatment-related effect on organ weights was found. The main histopathological effect consisted in inflammation of skin with parakeratosis or hyperkeratosis in both sexes at the two highest doses.

Concerning reproductive organs weights, only a slightly decreased absolute weight of ovaries was found at the highest dose but not in the satellite group. Histopathological effects in the male reproductive tract consisted in genital tract oedema of interstitium in prostate gland (2-5-3-0), inflammation of prostate gland (0-2-2-0) and inflammation of epididymis (1-1-2-1). Similar effects were observed in the satellite groups: genital tract oedema of interstitium in prostate gland in 1-4 males, inflammation of prostate gland 0-2 in males and inflammation of epidydimis in 1-2 males. In females, only hydrometra of uterus was recorded (3-2-2-1 in the main test and 1-2 in the satellite groups).

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Not evaluated in this dossier.

4.9 Germ cell mutagenicity (Mutagenicity)

Not evaluated in this dossier.

Based on the CSR, negative results were obtained in both *in vitro* and *in vivo* assays.

4.10 Carcinogenicity

Not evaluated in this dossier.

4.11 Toxicity for reproduction

This proposal is based exclusively on the 2 studies provided in the registration dossier.

Table 20: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
EU method B.34 / OECD 415 One generation reproduction toxicity study; oral route Wistar Han rats (10 ♂; 25♀/group) 0, 20, 80, 320 mg/kg bw/day	NOAEL parental = 80 mg/kg bw/day NOAEL reproduction = 80 mg/kg bw/day NOAEL development < 20 mg/kg bw/day	At 320 mg/kg bw/day - ↓ bw in males - ↓ absolute weight prostate - various damage of spermiogenesis - inflammation and/or erosion of digestive tract in both sexes - ↓ fertility, conception and gestation index - ↓ viability index - ↑ relative and absolute brain weight of pups From 80 mg/kg bw/day - late opening of eyes From 20 mg/kg bw/day - Vacuolisation of brain cell nuclei in pups	Plodíková, 2008
EU method B.31 Prenatal developmental toxicity study; oral route Wistar Han rats (24-25♀/group) 0, 20, 100, 500 mg/kg bw/day	NOAEL maternal = 20 mg/kg bw/day NOAEL developmental < 20 mg/kg bw/day	At 500 mg/kg bw/day - ↓ maternal bw - ↑ post-implantation losses - ↓ pup bw From 100 mg/kg bw/day - Erosion of digestive tract in dams From 20 mg/kg bw/day - decreased number of ossification sites in sternum - incomplete ossification of cervical vertebrae	Plodíková, 2009

4.11.1 Effects on fertility

4.11.1.1 Non-human information

In a one generation reproduction toxicity study performed according to EU method B.34 or OECD 415, 4 groups of Wistar Han rats (consisting in 10 males and 25 females) received potassium permanganate by oral gavage at dose levels of 0, 20, 80 and 320 mg/kg bw/day (Plodíková, 2008). Doses were selected on the basis of scientific literature information and with respect to the results of acute oral toxicity study, repeated dose oral toxicity study and *in vivo* micronucleus test.

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 died in the first week after mating.

Treatment resulted in a decreased parental body weight. In males, body weight was slightly decreased from 6th week of application in the low and medium dose groups. At 320 mg/kg bw/day, the body weight was markedly lowered from 1st week of treatment and was statistically significantly decreased at the end of the study. Negative body weight gain was found from week 11. This was associated with a slight decreased food consumption from 5th week of treatment at 20 and 80 mg/kg bw/day and from 3rd week of treatment at 320 mg/kg bw/day. This change was marked from 8th week.

Table 4.11.1.1-01. Body weight and body weight gain in males

Body weight and body weight increment (grams/animal/week)									
Average body weight					Average body weight increment				
Dose level mg/kg bw/day	0	20	80	320	Dose level	0	20	80	320
Before application	207.5	206.6	207.9	206.3 (-0.6%)	Before application	-	-	-	-
1st week	241.1	233.8	237.1	223.0 (-7.5%)	1st week	33.6	27.2	29.2	16.7
2nd week	261.1	255.9	257.1	240.3 (-8.0%)	2nd week	20.0	22.1	20.2	17.3
3rd week	284.3	275.9	280.8	257.6 (-9.4%)	3rd week	23.2	20.0	23.7	17.3
4th week	298.6	289.4	290.6	274.1 (-8.2%)	4th week	14.3	13.5	9.8	16.5
5th week	315.2	300.3	304.9	285.4 (-9.5%)	5th week	16.6	10.9	14.3	11.3
6th week	326.7	311.2	314.9	295.0 (-9.7%)	6th week	11.5	10.9	10.0	9.6
7th week	338.3	320.9	323.6	299.9 (-11.4%)	7th week	11.6	9.7	8.7	4.9
8th week	348.0	329.1	330.0	300.3 (-13.7%)	8th week	9.7	8.2	6.4	0.4
9th week	354.2	335.5	338.0	309.9 (-12.5%)	9th week	6.2	6.4	8.0	9.6
10th week	363.0	343.3	340.2	317.2 (-12.6%)	10th week	8.8	7.8	2.2	7.3
11th week	363.8	344.3	342.5	313.8 (-13.7%)	11th week	0.8	1.0	2.3	-3.4
12th week	368.2	345.8	347.6	310.7 (-15.6%)	12th week	4.4	1.5	5.1	-3.1
13th week	379.9	355.2	352.8	309.0* (-18.7%)	13th week	11.7	9.4	5.2	-1.7

*: values statistically significant on probability level 0.05 (ANOVA test)

In females, no significant effect on body weight was observed from the pre-mating period to lactation between treated and control groups. Non-pregnant females and aborted females were not included in calculation of average weight increment and average food of pregnant females. Body weight gain was negative at the end of the 1st week of application at 320 mg/kg bw/day. During pregnancy, a slight decreased body weight gain was reported at 80 mg/kg bw/day (end of 2nd week) and at 320 mg/kg bw/day (end of 1st week and 2nd week). Only between the 1st to 4th day of lactation, body weight gain was slightly decreased at 20 and 320 mg/kg bw/day. Decrease of body weight and loss of body weight gain were recorded at the end of lactation (from 14th to 21st day) in all groups, including control.

This was associated with decreased food consumption during pre-mating at 320 mg/kg bw/day (only at the end of 1st week) and during whole lactation period in all treated groups. More marked decrease was registered at 20 and 320 mg/kg bw/day than at 80 mg/kg bw/day.

Table 4.11.1.1-02. Body weight and body weight gain in females

Body weight and body weight increment (grams/animal/week)										
Average body weight						Average body weight increment				
Dose level (mg/kg bw/day)		0	20	80	320	Dose level	0	20	80	320
Before mating	Before application	188.7	187.6	188.3	188.0 (-0.5%)	Before application	-	-	-	-
	1st week	195.1	195.7	195.7	186.9 (-4.2%)	1st week	6.4	8.1	7.4	-1.1
	2nd week	202.9	200.5	201.9	200.5 (-1.2%)	2nd week	7.8	4.8	6.2	13.6
		Mating period					Mating period			
Day of pregnancy	0	208.3	206.9	213.9	212.2 (+1.8%)	0	-	-	-	-
	7	227.0	224.2	233.8	226.7 (-0.1%)	7	18.7	17.3	19.9	14.5
	14	254.5	249.7	254.3	250.6 (-1.5%)	14	27.5	25.5	20.5	23.9
	21	315.2	304.7	312.2	301.9 (-4.2%)	21	60.7	55.0	57.9	60.3
Day of lactation	0	236.3	237.6	241.0	245.2 (+3.6%)	0	-	-	-	-
	4	255.5	252.9	263.9	258.9 (+1.3%)	4	19.2	15.3	22.9	13.7
	7	269.8	265.4	276.9	273.7	7	14.3	12.5	13.0	14.8

					(+1.4%)					
	14	284.5	278.0	290.6	287.7 (+1.1%)	14	14.7	12.6	13.7	14.0
	21	272.3	265.9	275.6	279.1 (+2.4%)	21	-12.2	-12.1	-15.0	-8.6

Health condition was good at 20 mg/kg bw/day in both sexes and at 80 mg/kg bw/day in females. At 80 mg/kg bw/day, 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 in 3 animals at 1st week, in 2 animals at 2nd week, in one animal at 4th week and in 2 animals at 7th week.

Macroscopical and microscopical examination in males:

Reduced testes, prostate gland, epididymides or seminal vesicle were observed sporadically. All males at the highest dose level showed marked changes in the stomach – blood erosions of mucosa. At this same dose, erosions of duodenum were seen in 2 males, dilatation of stomach in one male or changed mucous membrane in 2 males or liver affections (changed colour, angustate periphery of lobes, congested). These findings were treatment-related.

Organ weight analysis revealed a statistically significantly decrease of absolute weight of prostate gland at 320 mg/kg bw/day. The relative weight was also decreased but not statistically significant. Slight decreased absolute weight of testes and epididymides (without statistical significance) was also recorded at the highest dose.

Histopathological changes were recorded in digestive system. Erosions, ulcerations and haemorrhage in the stomach mucosa or submucosa and inflammation in stomach, forestomach and duodenum were diagnosed.

Effects were also reported in testes, epididymides and prostate gland. 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 epipidymides were increased at the highest dose, in comparison to other groups (see table 4.11.1.1-03).

Table 4.11.1.1-03. Microscopic findings in males

Pathological findings*	Dose level (mg/kg bw/day)			
	0	20	80	320
Number of examined animals	10	10	10	10
Without pathological changes	3	4	2	0
PROSTATE GLAND – inflammation, lymphocyte infiltration or edema of interstitium	2	2	5	3

EPIDIDYMIDES – vacuolar dystrophy	0	2	0	0
EPIDIDYMIDES – inflammation	1	0	2	0
EPIDIDYMIDES – decreased number of spermiocytes, presence of necrotic cell	0	1	0	3
TESTES – inflammation	1	0	0	0
TESTES – haemorrhage	0	0	0	1
TESTES – atrophic germinative epithelium	3	0	3	1
TESTES – insignificant damage of spermiogenesis	1	2	0	0
TESTES – slight damage of spermiogenesis	0	0	0	5
TESTES – moderate damage of spermiogenesis	0	0	0	2
TESTES – important damage of spermiogenesis	0	1	0	0
TESTES – atrophy or decreased quantity of Leydig cells	0	1	0	1
STOMACH – erosion, ulceration or haemorrhage	0	0	1	8
STOMACH – inflammation or inflammatory infiltration	0	0	1	10
FORESTOMACH – inflammation or inflammatory infiltration	0	0	1	6
DUODENUM – haemorrhage	0	0	0	1
DUODENUM – oedema, inflammatory infiltration	0	0	0	2
LIVER – dilatation or sinuses	0	0	0	1

*No statistical analysis was performed on these findings in the study report.

Macroscopical and microscopical examination in females:

At 320 mg/kg bw/day, nine females showed bleeding erosions of stomach mucosa and one female also have blood in duodenum or liver affections. These findings were treatment-related. Dilatation of uterus was more numerous at the highest dose level than in other groups.

Relative and absolute organ weights were comparable between treated and control groups.

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 reproductive system, ovaries and uterus were affected. 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 (see table 4.11.1.1-04).

Table 4.11.1.1-04. Microscopic findings in females

Pathological findings*	Dose level (mg/kg bw/day)

	0	20	80	320
Number of examined animals	25	25	25	25
Without pathological changes	2	3	1	3
PITUITARY GLAND – cysts	0	1	1	0
UTERUS – hydrometra	5	0	1	7
UTERUS – cell hyperplasia of endometrium	13	15	14	9
UTERUS – extinction of endometrial glands	0	0	0	1
UTERUS – atrophy of endometrium	3	0	2	5
UTERUS – fibrosis of endometrium	0	0	0	1
VAGINA – atrophic epithelium	0	0	1	0
OVARIES – follicular cysts	20	16	21	13
OVARIES – cell hyperplasia of stroma	2	0	2	3
OVARIES – cystic degenerations of follicles	0	0	1	0
STOMACH – erosions, ulceration or haemorrhage	0	0	0	5
STOMACH – inflammation or inflammatory infiltration	0	0	0	9
FORESTOMACH – inflammation or inflammatory infiltration	0	0	0	3
LIVER – mononuclear infiltration	0	0	0	1

*No statistical analysis was performed on these findings in the study report

Reproduction parameters:

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[1] and conception index[2] 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.

Table 4.11.1.1-05. Reproduction data

Observed parameters*	Dose level (mg/kg bw/day)			
	0	20	80	320
Males paired	10	10	10	10
Females paired	25	25	25	25
Females mated	25	25	25	25

[1] Fertility index (%) = no. of pregnant females/no. of females paired x 100 (the pregnancy was determined by the presence of spermatozoa in vaginal smear)

[2] Conception index (%) = no. of pregnant females rats/no. of females mated x 100 the pregnancy was determined by the presence of spermatozoa in vaginal smear)

Females pregnant	21	21	20	16
Mothers bearing live pups	19	17	17	11
Number of born pups	213	168	178	101
Number of live born pups	207	164	163	99
Average duration of pregnancy	22.1	22.2	22.5	22.1

*No statistical analysis was performed on these findings in the study report

Table 4.11.1.1-06. Fertility parameters

Calculated parameters*	Dose level (mg/kg bw/day)			
	0	20	80	320
Percentage of mating	100	100	100	100
Fertility index	84	84	80	64
Conception index	84	84	80	64
Gestation index	90.5	81	85	68.8
Percentage of live males at first check of litter	48.5	54.0	46.9	56.6
Percentage of live females at first check of litter	51.5	46.0	53.1	43.4
Percentage of postnatal loss	4.4	3.1	10.5	6.1
Percentage of pre-weaning loss	0	0	0	1.1
Percentage of live males at weaning	48.5	54.0	47.2	56.4
Percentage of live females at weaning	51.5	46.0	52.8	43.6
Viability index	98.6	99.4	98.8	96.0
Weaning index	100	100	100	98.9

*No statistical analysis was performed on these findings in the study report

Observation of pups:

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.

Table 4.11.1.1-07. Number of live pups and sex

Dose level (mg/kg bw/day)	0		20		80		320	
Day after birth	Total number (average)	Number of M and F	Total number (average)	Number of M and F	Total number (average)	Number of M and F	Total number (average)	Number of M and F
1	204 (10.7)	5.2 M 5.5 F	163 (9.6)	5.2 M 4.4 F	162 (9.5)	4.5 M 5.1 F	99 (9.0)	5.1 M 3.9 F
4	204 (11.3)	5.5 M 5.8 F	163 (9.6)	5.2 M 4.4 F	161 (10.1)	4.8 M 5.3 F	95 (9.5)	5.4 M 4.1 F
7	204 (11.3)	5.5 M 5.8 F	163 (9.6)	5.2 M 4.4 F	161 (10.1)	4.8 M 5.3 F	95 (9.5)	5.4 M 4.1 F
14	204 (11.3)	5.5 M 5.8 F	163 (9.6)	5.2 M 4.4 F	161 (10.1)	4.8 M 5.3 F	94 (9.4)	5.3 M 4.1 F
21	204 (11.3)	5.5 M 5.8 F	163 (9.6)	5.2 M 4.4 F	161 (10.1)	4.8 M 5.3 F	94 (9.4)	5.3 M 4.1 F

M: males; F: females

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.

At macroscopic examination, sporadic pathological findings were recorded at the highest dose: missing testes and epididymides (one pup), one testis reduced (one pup) and stomach mucous membrane congested and chyme with blood (two pups).

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 treated groups compared to control.

Table 4.11.1.1-08. Effect on brain in pups

Parameter	Dose level (mg/kg bw/day)			
	0	20	80	320
Number of examined pups	20	20	20	20
Absolute weight of brain (g)	1.28	1.32	1.30	1.35*
Relative weight of brain (g)	3.34	3.35	3.50	3.68*
Microscopic findings (number of pups with changes)				

Without changes	17	1	2	2
Vacuolisation of cell nuclei (mild)	3	7	3	2
Vacuolisation of cell nuclei (more marked)	0	12	15	16

*: values statistically significant on probability level 0.05 (ANOVA test)

4.11.1.2 Human information

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

In a prenatal developmental toxicity study performed according to EU method B.31 or OECD 414, 4 groups of Wistar Han rats (consisting in 24-25 females) 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 (Plodíková, 2009). Doses were selected on the basis of a 28 day repeated-dose toxicity study and a one generation reproduction toxicity study.

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. This was associated with lower food consumption from 8th to 14th day of gestation, effect more marked at 500 mg/kg bw/day.

Table 4.11.2.1-01. Body weight

Body weight in grams (average ± standard deviation)				
Day of pregnancy	Dose level			
	0	20	100	500
1st day	183.89±12.64	185.17±11.45	179.61±13.53	184.03±12.59 (+0.08%)
5th day	194.25±13.77	196.52±12.49	191.26±14.77	195.93±14.75 (+0.8%)
8th day	201.72±14.55	203.09±12.67	197.78±15.62	173.41±19.55* (-14%)
11th day	211.17±15.09	213.26±14.57	208.51±17.09	185.05±18.12* (-12.4%)
14th day	221.96±16.39	223.91±13.79	218.68±18.59	198.93±19.89* (-10.3%)
17th day	243.58±21.66	243.96±18.02	237.62±21.24	221.59±20.41* (-9.0%)

20th day	272.37±28.62	269.98±25.04	262.64±26.47	251.62±25.02 (-9.0%)
Average increment	88.48	84.81	83.03	67.59

* values statistically significant on probability level 0.05 (ANOVA test)

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 application (emesis, return of the test substance into oesophagus) and excited behaviour immediately after application 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.

Table 4.11.2.1-02. Biometry of uterus

Parameters	Dose level (mg/kg bw/day)			
	0	20	100	500
Necropsy body weight of female (g)	272.37	269.98	262.64	251.62
Absolute weight of uterus (g)	53.16	46.23	42.93	41.95
Relative weight of uterus (%)	19.30	17.00	15.95	16.41

During necropsy, no effect was observed in the control group and at the low dose level. At 100 mg/kg bw/day, only 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.

Table 4.11.2.1-03. Parameters of reproduction

Parameters of reproduction (number per females, averages)*				
Parameters	Dose level (mg/kg bw/day)			
	0	20	100	500
Implantations	9.13	8.95	8.19	8.57
Resorptions	0.61	1.59	1.38	2.83
Corporea lutea	11.57	12.18	11.24	11.43

*No statistical analysis was performed on these findings in the study report

Table 4.11.2.1-04. Pre and post-implantation losses

Pre and post-implantation losses (% per female, average)*				
Parameter	Doses level (mg/kg bw/day)			
	0	20	100	500
Pre-implantation loss	22.84	25.61	28.39	25.49
Post-implantation loss	14.18	22.80	24.65	42.25

*No statistical analysis was performed on these findings in the study report. However, when a Kruskal Wallis test is performed, the increase of post-implantation loss is statistically significant at the highest dose.

The number of live foetuses was slightly decreased at 100 and 500 mg/kg bw/day but without dose dependency or statistical significance.

Table 4.11.2.1-05. Number of foetuses in litter (average per dose group)

Parameters	Dose level (mg/kg bw/day)			
	0	20	100	500
Total number of live foetuses	9.80	9.16	8.41	8.80
Number of live fetuses – males	5.05	5.16	4.47	4.80
Number of live fetuses – females	4.75	4.00	3.94	4.00
Number of dead fetuses	0.00	0.05	0.00	0.00

Foetuses body weight was decreased, with statistical significance only reported for females at the highest dose level.

Table 4.11.2.1-06. Body weight of foetuses (grams, averages)

Parameters	Dose level (mg/kg bw/day)			
	0	20	100	500
Weight of foetus	3.51	3.19	3.19	2.97
Weight of male foetus	3.57	3.21	3.20	3.00
Weight of female foetus	3.45	3.13	3.12	2.78*

* values statistically significant on probability level 0.05 (ANOVA test)

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 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.

Table 4.11.2.1-07. Skeletal alteration (number of affected foetuses / %)

Alteration	Dose level			
	0	20	100	500
Total number of examined foetuses	101	91	78	67
Cranium – absence of supraoccipital bone	0 0%	0 0%	0 0%	1 1.5%
Cranium – unossified of supraoccipital bone	0 0%	1 1.1%	0 0%	0 0%
Cranium – incomplete ossification of parietal bone	3 3%	0 0%	8 10.3%	1 1.5%
Cranium – incomplete ossification of frontal bone	0 0%	0 0%	2 2.6%	0 0%
Cranium – incomplete ossification of interparietal bone	1 1%	0 0%	0 0%	0 0%
Sternum – decreased number of ossification sites	40 39.6%	49 53.8%	48 61.5%	45 67.2%
Vertebrae – incomplete ossification of cervical vertebrae	0 0%	8 8.8%	8 10.3%	12 17.9%
Vertebrae – unossified sacral vertebrae	5 5.0%	18 19.8%	8 10.3%	11 16.4%
Ribs – wavy (undulation along the length of a rib)	7 6.9%	3 3.3%	6 7.7%	0 0%

Table 4.11.2.1-08. Skeletal alteration (number of litters with affected foetuses / %)

Alteration	Dose level			
	0	20	100	500
Total number of examined foetuses	20	19	17	14
Cranium – absence of supraoccipital bone	0 0%	0 0%	0 0%	1 7.1%
Cranium – unossified of supraoccipital bone	0 0%	1 5.3%	0 0%	0 0%

Cranium – incomplete ossification of parietal bone	2 10%	0 0%	5 29.4%	1 7.1%
Cranium – incomplete ossification of frontal bone	0 0%	0 0%	1 5.9%	0 0%
Cranium – incomplete ossification of interparietal bone	1 5%	0 0%	0 0%	0 0%
Sternum – decreased number of ossification sites	13 65%	14 73.7%	14 82.4%	12 85.7%
Vertebrae – incomplete ossification of cervical vertebrae	0 0%	2 10.5%	2 11.8%	4 28.6%
Vertebrae – unossified sacral vertebrae	1 5%	4 21.1%	2 11.8%	3 21.4%
Ribs – wavy (undulation along the length of a rib)	6 30%	3 15.8%	4 23.5%	0 0%

In the study report, the above 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.

4.11.2.2 Human information

No data

4.11.3 Other relevant information

No data

4.11.4 Summary and discussion of reproductive toxicity

In a one generation toxicity study, potassium permanganate induced parental effects at 320 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. The primary target organ was the digestive tract with inflammation, erosion, ulceration or haemorrhage. Regarding to reproductive organs, a significant decreased weight of prostate gland and various damages of spermatogenesis were observed. There were no significant pathological effects which indicated damage to female reproductive organs.

Concerning reproductive parameters, decrease of fertility, conception and gestation index were recorded at 320 mg/kg bw/day. This result showed decreased ability of the animals to achieve or maintain a pregnancy.

In pups, the target organ is the brain with increased weight at 320 mg/kg bw/day and marked vacuolisation of cell nuclei in cortex and/or hippocampus in all treated groups. Other effects included a slight decrease of viability index at 320 mg/kg bw/day and a late opening of eyes from 80 mg/kg bw/ day.

In a prenatal developmental toxicity study, body weights of dams and pups were significantly decreased at 500 mg/kg bw/day. This dose also induced a 3 fold increase of post-implantation loss and an increase of total resorptions. Decreased number of ossification sites in sternum and incomplete ossification of cervical vertebrae were observed in all treated groups (doses starting at 20 mg/kg bw/day).

4.11.5 Comparison with criteria

When administered to rats, potassium permanganate induced effects on sexual organs and function:

In males, damage of spermatogenesis was observed in the presence of significant decreased body weight (up to 18.7%) and irritation of the digestive tract 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 male effect. 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 effects were observed in females, however, 9 females out of 25 were found to be not pregnant. There was no significant decreased body weight and inflammation and/or erosion of stomach or forestomach was observed in 10/25 females. 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 of pregnant females cannot not be considered a secondary non-specific consequence of general toxicity.

Since the adverse effects as slight to moderate damage of spermiogenesis and decreased fertility index were only observed at a high dose causing systemic toxicity, the evidence is not sufficiently convincing to place the substance in Category 1. However, it is considered that these effects fulfill the criteria for reproductive toxicity category 2 set in the CLP regulation.

When administered by oral route to rats, potassium permanganate induced effects on development:

In the one generation study, 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 decreased 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.

In the prenatal toxicity study, decreased pup body weight was reported in all treated groups. This was statistical 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.

A classification for reproductive toxicity category 1B is proposed 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. Therefore, because the effects are severe and not considered as a non-specific consequence of maternal toxicity, the evidence is sufficient to propose a classification 1B and not a Category 2. Other developmental effects of lower severity (late opening of eye, skeletal variation and histopathological effects on pup brain) were also reported and occurred at doses not associated with maternal toxicity. Since they were not related to a decreased pup body weight, it can be hypothesized that they are not related to a delay of development. All these effects were considered relevant to humans, although no specific mode of action can be proposed from the available data.

4.11.6 Conclusions on classification and labelling

When administered to rats, potassium permanganate induced effects on sexual organs and function. In a one generation toxicity study, potassium permanganate induced a significant decreased weight of prostate gland and various damages of spermatogenesis. These effects occurred at a dose associated with decreased body weight and irritation of digestive tract. Decrease of fertility index was also recorded, showing a decreased ability of the animals to achieve a pregnancy. It can be hypothesized that the decreased number of pregnant females is related to the effects on spermatogenesis. However, considering that only slight or moderate damage of spermiogenesis was observed, it is not clear if the effects on testes were sufficient to explain the decrease of fertility. Therefore, it cannot be excluded that the decreased fertility index was, at least partially, female dependent. Considering the low systemic effects noted in females, the decreased number of pregnant females cannot be considered a secondary non-specific consequence of general toxicity.

Since the adverse effects are slight to moderate damages of spermiogenesis and because decreased fertility index were only observed at a high dose causing systemic toxicity, the evidence is not sufficiently convincing to place the substance in Category 1 for fertility endpoint. However, a classification for reproductive toxicity category 2 is judged appropriate.

When administered to rats, potassium permanganate induced effects on development. In a one generation study, decreased gestation index was observed. This is consistent with the increase of post-implantation loss and resorption reported in a prenatal toxicity study. Other developmental effect

observed in the one generation study included vacuolisation of cell nuclei in cortex and/or in hippocampus and a late opening of eyes occurring at doses not associated with maternal toxicity or with a decreased pup body weight.

In the prenatal developmental toxicity study, decreased pup body weights and skeletal abnormalities (decreased number of ossification sites in sternum and incomplete ossification of cervical vertebrae) were also observed.

A classification for reproductive toxicity category 1B is proposed for developmental endpoint based on the low gestation index and high rate of post-implantation losses. Indeed, since the effects are severe and not considered as a non-specific consequence of maternal toxicity, the evidence is sufficient to propose a Category 1B and not place the substance in Category 2. Other developmental effects of lower severity (late opening of eye, skeletal variation and histopathological effects on pup brain) were also reported and occurred at doses not associated with maternal toxicity and were not related to a decreased pup body weight.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Effects on sexual function and fertility

The Dossier Submitter (DS) proposed a harmonised classification and labelling of potassium permanganate as Repr. 2 for effects on sexual function and fertility.

A one-generation reproductive toxicity study in rats (Plodicová, 2008, OECD TG 415 and GLP compliant) and two 28-day studies, one with oral and one with dermal exposure to potassium permanganate (OECD TG 408, GLP), were included in the CLH report by the DS for the assessment of effects on sexual function and fertility.

In the one-generation study Wistar rats were exposed to 0, 20, 80 and 320 mg/kg bw/d of potassium permanganate. Some reproductive parameters were impaired. These included a markedly lower number of pregnant females and number of dams bearing live pups at the highest dose level. Decreased fertility index, conception index and gestation index was also reported at 320 mg/kg bw/d. Other reproductive parameters such as average duration of pregnancy, post-implantation losses and pup viability index were not adversely affected. Effects reported in the reproductive organs in the one-generation study were a significant decreased weight of prostate gland and various damages of spermatogenesis. There were no significant pathological findings which indicated damage to female reproductive organs.

Parental toxicity included a reduced body weight and body weight gain in both sexes with a significant effect in males. This was associated with reduced food consumption. The primary target organ was the digestive tract with inflammation, erosion, ulceration or haemorrhage. However, in 5 of the 9 females in the high dose group that were not pregnant, no effects on the digestive tract were reported.

In the 28-day oral study rats were exposed to 0, 40, 100 and 250 mg/kg bw/d of potassium permanganate. Two satellite groups were also included and exposed to 0 or 250 mg/kg bw/d

of potassium permanganate for 28 days with a recovery period of 14 days. In the male reproductive organs an increased relative weight of testes and epididymis was reported at 100 and 250 mg/kg bw/d. These effects were not reported in the satellite groups. Histopathological effects in the male reproductive tract were only sporadic and not dose-related.
In females an increase in absolute and relative weight of uterus was reported in all dose groups including the satellite treated groups. Histopathological effects in the female reproductive tract were only sporadic and not dose-related.

Systemic toxicity in the 28-day study included a slight decrease in body weight at all doses in males and at the highest dose in females. Decreased body weight gain was also reported at all doses in males and at the two highest doses in females. These effects were associated with a decrease in food consumption. The water consumption was also decreased at 250 mg/kg bw/d in males and females. Variations in haematology, biochemistry and urinalysis were reported, in some animals from 100 mg/kg bw/d. The relative weight of the liver was increased in all dose groups in males. The spleen weight (relative and absolute) was increased in males and females in the high dose group. In females the kidney weight (relative and absolute) was also increased in the high dose group. Microscopic examination showed effects in the liver and stomach in both sexes. In 6 females eosinophil infiltration and oedema of mucosa were reported in the stomach in the high dose group; however, similar effects were not reported in the other groups. Only sporadic changes were reported in males in the liver and stomach.

In the 28-day dermal repeated dose toxicity study, rats were exposed to 0, 150, 300 and 600 mg/kg bw/d. Two satellite groups were also included exposed to 0 or 600 mg/kg bw/d of potassium permanganate for 28 days with a recovery period of 14 days. No marked effects were reported in male and female reproductive organs. Systemic toxicity was evident as a slight decrease in body weight with a more marked decrease in body weight gain at all dose levels in both sexes. This was associated with no or low reduction in food consumption. Some variations in urinanalysis, haematology and biochemistry were also reported in both sexes. No statistically significant changes in organ weight were reported, and the main histopathological effects included inflammation of skin with parakeratosis or hyperkeratosis in both sexes in the mid- and high dose group.

Overall, the DS concluded that the adverse effects to the male reproductive organs were slight to moderate and that the data does not establish a link between the effects on the male reproductive organs and the decrease in fertility index. Further, the decreased fertility index was only observed in the high dose group which also caused systemic toxicity. The evidence was therefore not sufficiently convincing to place potassium permanganate in Repr. 1B for effects on sexual function and fertility. However, a classification for reproductive toxicity in Repr. 2 was proposed.

Developmental toxicity

The DS proposed a harmonised classification and labelling of potassium permanganate as Repr. 1B for effects on development.

A prenatal developmental toxicity study performed according to OECD TG 414 and GLP compliant (Plodíková, 2009) and the one-generation reproduction toxicity study (Plodíková, 2008) in rats were included by the DS to assess the developmental toxicity of potassium permanganate.

In the developmental toxicity study, Wistar rats were exposed to 0, 20, 100 and 500 mg/kg bw/d of potassium permanganate from gestation day (GD) 5-19 (Plodíková, 2009). In this study the body weight of the female pups were statistically significantly decreased at 500 mg/kg bw/d. This dose also induced a 3-fold increase in post-implantation loss and an increase in total resorptions. A decreased number of ossification sites in sternum and incomplete ossification of cervical vertebrae were also observed in all treated groups. Maternal toxicity was noted as decreased body weight in the high dose group, and several clinical signs and microscopic changes in the stomach in the mid- and high dose groups.

In the one-generation reproductive toxicity study Wistar rats were exposed to 0, 20, 80 and 320 mg/kg bw/d of potassium permanganate. In this study the gestation index was 68.8% in the high dose group compared to 90.5% in the controls. In the pups the target organ was the brain with an increased weight at 320 mg/kg bw/d and marked vacuolisation of cell nuclei in cortex and/or hippocampus in all treated groups. Other effects included a slight decrease of viability index at 320 mg/kg bw/d and late opening of eyes from 80 mg/kg bw/d. Maternal toxicity was noted as microscopic changes in the stomach. However, in 5 of the 9 females in the high dose group that were not pregnant no effects on the digestive tract were reported.

Overall, the DS considered that based on the low gestation index (68.8%) and high incidence of post-implantation losses (42%) a classification for developmental toxicity as Repr. 1B; H360D was justified. The DS also noted that these effects were only reported in the high dose in the one-generation study (320 mg/kg bw/d) and in the developmental toxicity study (500 mg/kg bw/d). However, since these doses were not associated with excessive parental toxicity, the effects reported at these dose levels were considered relevant for classification. The DS considered the effects as severe and not as a non-specific consequence of maternal toxicity. Other developmental effects of less severity (late opening of eye, skeletal variations and effects on pup brain) were also reported and occurred at doses not associated with maternal toxicity. The evidence was therefore considered sufficiently convincing and the DS proposed a classification of potassium permanganate for developmental toxicity as Repr. 1B; H360Df.

Comments received during public consultation

Three Member States Competent Authorities (MSCAs) and one Company-Manufacture commented on the CLH report during public consultation.

One MSCA supported the classification proposed by the DS as Repr. 1B; H360Df. One MSCA questioned the classification as Repr. 1B for developmental effects and thought that maybe a classification as Repr. 2 for both fertility and development was more appropriate based on the available data. One MSCA agreed with the DS's proposal for a classification as Repr. 1B for developmental toxicity but suggested also a classification for fertility in category 1B based on the important effects on the fertility parameters.

Two of the MSCAs asked for more clarification regarding the parental toxicity and the influence of the parental toxicity on the effects reported in the Plodíková, 2008 and 2009 studies.

Another MSCA asked for more data on the toxicokinetic properties of KMnO4 for a possible read-across from other tested manganese-oxidated forms. Given the strong oxidating potential, it is expected that a reduced form of Mn will be formed in the stomach. A clarification regarding

the statistical significance of the effects in the Plodíková, 2008 and 2009 studies was also requested.

The Company-Manufacturer commented and did not support the classification proposed by the DS. They commented that many studies are available on manganese including inorganic compounds which were not assessed by the DS and which showed no effects on reproduction. The only two reproductive toxicity studies included by the DS were considered by the Company-Manufacturer to lack relevant parameters such as statistical analysis and information on historical control data. Furthermore the studies were also conducted at very high dose levels, thereby questioning their reliability. Therefore, as a precautionary approach they proposed a self-classification as STOT RE 2 based on the general toxicity reported in the reproductive toxicity studies and in the 28-day repeated dose toxicity studies included in the CLH report. They also proposed a harmonised classification as Repr. 2; H361d as there is some evidence of developmental toxicity, although not conclusive, and no classification for sexual function and fertility with the argument that effects on fertility occurred at high doses and as a secondary consequence of general toxicity.

Additional key elements

Effects on fertility following exposure to other manganese compounds

Several other studies in mice have reported effects on male reproductive organs, sperm quality and fertility following exposure to manganese compounds. Some of these studies are summarised below.

An oral fertility study in Swiss mice was performed by Elbethieha (2001) where the male and female mice had a 12-week treatment with manganese (II) chloride tetrahydrate followed by a 10-day mating period and after the mating period the animals were left for 10 more days before they were sacrificed. The results from the study are shown in the table below:

Table: Effects on fertility following exposure to manganese (II) chloride tetrahydrate in male and female Swiss mice

$MnCl_2$ $4H_2O$ in drinking water	Control	1000 mg/L	2000 mg/L	4000 mg/L	8000 mg/L
Treated males/ non-treated females	-	**108.3**±6.34 mg/kg bw/d	**172**±13.02 mg/kg bw/d	**352**.±14.91 mg/kg bw/d	**706.5**±18.26 mg/kg bw/d
No. of pregnant females	26/28 (92%)	25/28 (89%)	22/28 (78%)	20/28 (71%)	**17/28 (66%)***
No. of implantations	9.00±2.22	8.73±1.68	8.86±1.75	8.15±1.81	8.00±1.96
No. of viable foetuses	8.76±3.35	8.50±1.74	8.40±2.23	7.60±1.87	7.70±1.89
Total no. of resorptions	7	13	10	11	6
Treated females/ non-treated males	-	**99.83**±8.61 mg/kg bw/d	**187.54**±9.34 mg/kg bw/d	**358.84**±14.16 mg/kg bw/d	**634.92**±21.52 mg/kg bw/d
No. of pregnant females	13:15 (86%)	13:15 (86%)	13:15 (86%)	9:15 (60%)	10:15 (66%)

No. of implantations	9.41±1.68	9.08±1.62	8.42±1.92	8.43±2.38	**7.80±1.55***
No. of viable foetuses	9.41±1.68	9.00±1.68	8.25±2.05	8.28±2.22	**7.60±1.58***
No. of mice with resorptions	0/13 (0.0%)	3/13 (23%)	2/13 (15%)	1/9 (11%)	2/10 (20%)
Total no. of resorptions	0	3	2	1	2
Body weight	34.6±6.08	32.84±5.12	33.31±3.40	33.21±3.02	33.33±4.53
Ovarian weights	2.12±0.83	2.5±0.74	2.4±0.79	**3.50±1.06***	**4.70±2.3***
Uterine weights	23.60±8.51	**31.80±1.28***	**34.50±8.12***	**35.50±6.9****	**33.7±9.7***

Fertility was significantly reduced in males exposed to 8000 mg/L manganese chloride, and was reduced, although not statistically significantly, when females were exposed to 4000 mg/L and 8000 mg/L. However, the number of implantation sites and viable foetuses were significantly reduced in females exposed to $MnCl_2$ at 8000 mg/L but not at the lower concentrations. The reduction in the number of implantations and viable foetuses may be due to poor development of fertilized ova and/or to some modification of the uterine lining function before the arrival of the embryo.

An oral fertility study in male CD mice was performed by Ponnapakkam (2003). The male mice were exposed by gavage to manganese acetate at doses of 0, 7.5, 15.0 and 30.0 mg/kg bw/d for 43 days and were assessed for effects on male reproductive organs and fertility, see the three tables below.

Table: Effects in male mice following exposure to manganese acetate on male reproductive organs

	Vehicle control	Treated	Treated	Treated	Control
	0 mg/kg bw/d	7.5 mg/kg bw/d	15 mg/kg bw/d	30 mg/kg bw/d	-
Initial bw (g)	32.38 ± 0.87	31.69 ± 0.98	31.05 ± 0.91	30.24 ± 0.85	30.78 ±0.95
Final bw (g)	39.28 ± 1.29	35.05 ± 2.63	39.37 ± 1.21	36.0 ± 1.12	39.83 ± 1.38
Right testis absolute weight (mg)	137.12 ± 5.41	139.05 ± 0.71	135.6 ± 5.53	133.55 ± 5.62	133.27 ± 4.04
Right testis relative weight (%)	0.35	0.40	0.34	0.37	0.34
Left testis absolute weight (mg)	131.58 ± 8.81	130.44 ± 3.47	129.25 ± 6.45	127.65 ± 5.26	128.96 ± 4.95
Left testis relative weight (%)	0.33	0.37	0.33	0.35	0.32
Right epididymis abs. weight (mg)	68.04 ± 4.06	63.59 ± 2.82	68.40 ± 4.07	**70.67 ± 3.00***	69.94 ± 2.27
Right epididymis relative weight (%)	0.17	0.18	0.17	0.20	0.18
Left epididymis	61.22 ± 2.12	65.56 ± 1.92	69.60 ± 4.94	**71.15 ± 3.60***	71.30 ± 2.10

abs. weight (mg)					
Left epididymis relative weight (%)	0.16	0.19	0.18	0.20	0.18
Right cauda abs. weight (mg)	16.94 ± 1.06	17.49 ± 0.99	18.47 ± 0.58	18.07 ± 0.60	18.82 ± 0.23
Right cauda relative weight (%)	0.04	0.05	0.05	0.05	0.047
Left cauda abs. weight (mg)	17.23 ± 0.95	17.4 ± 1.08	18.78 ± 1.19	16.69 ± 0.94	18.28 ± 0.83
Left cauda relative weight (%)	0.04	0.05	0.05	0.05	0.05

Table: Effects in male mice following exposure to manganese acetate on spermatogenesis (compared to control)

	Treated	Treated	Treated
	7.5 mg/kg bw/d	15 mg/kg bw/d	30 mg/kg bw/d
Spermatogonia	no effect	no effect	no effect
Spermatocytes	no effect	no effect	no effect
Spermatids	no effect	no effect	no effect
Sperm appearance	no effect	no effect	no effect
Caudal sperm counts	↓	↓	↓
Testicular sperm counts	↓***	↓***	↓***
Sperm motility	↓	↓***	↓***

***P <0.001

Table: Male fertility - males 43 days treatment with manganese acetate/mating/detection of sperm plug (day 0 of pregnancy) / females sacrificed on the 18th day of gestation

	Control negative female mated with control negative male	Control female mated with high dose treated male (30 mg Mn/kg bw/d)
Males (n)	16	16
Females (n)	16	16
Pregnant (n)	15	13
Fertility (%)[a]	94	81
Average number of implantation sites	12.75 ± 0.92	11.70 ± 0.58
Average number of resorptions	0	0.2 ± 0.2
Average number of foetus/litter	12 ± 0.66	11 ± 0.64
Average number of live foetuses/litter	12 ± 0.66	11 ± 0.64
Average number of dead foetuses/litter	0	0
Average foetal weight/litter (mg)	17.0 ± 1.63	16.0 ± 1.92
Average number of corpora lutea/litter	12.12 ± 0.72	10.6 ± 0.90

[a](Pregnant/females mated) x 100

In this study exposure to manganese acetate caused a statistically significant ($p<0.001$) decrease in sperm motility at 15.0 and 30.0 mg/kg bw/d, and decreased sperm counts at 7.5, 15.0 and 30.0 mg/kg/d. However, there were no alterations in the fertility or pathology of the testicular tissue in the manganese-treated mice when compared with the controls.

An oral chronic study in Long-Evans rats with exposure to Mn_3O_4 was performed by Laskey *et al.* (1982). In this study Mn_3O_4 was given in food with sufficient Fe to pregnant nulliparous rats, with treatment starting from day 2 of pregnancy to the end of study (224 days of age). Non-litter mate males and females from each dose group were randomly selected, weighed and killed at 24, 40, 60, 100 or 224 days of age. Non-litter mates were mated at day 90-100 of age in each dose group, the pups were weighed, uterine implantation sites counted, the ovaries removed, and the corpora lutea counted. The results from the study are shown in the two tables below:

Table: Reproductive parameters in rats exposed chronically to Mn_3O_4

Laskey 1982 (Mn3O4) food Long-Evans rats	Control	350 ppm	1050 ppm	3050 ppm
	-	**16-32** mg/kg bw/d	**44-88** mg/kg bw/d	**158-316** mg/kg bw/d
Body weight	-	not affected at any age	not affected at any age	not affected at any age
Ovary weight	-	not affected	not affected	not affected
Testis weight	-	not affected	not affected	not affected
Percent pregnant [No. of females bred]	84 [43]	84 [45]	79 [47]	**63*** [24]
Litter size [No. of litters]	10.5 [20]	10.4 [19]	9.8 [20]	10.6 [10]
Ovulations (average per dam)	15.6	15.2	14.5	15.0
Resorptions (average per litter)	2.2	1.6	2.6	1.6
Preimplantation deaths (average per litter)	2.9	3.2	2.1	2.8
Mean F2 foetal weights (g) males	5.7	6.0	6.0	6.1
Mean F2 foetal weights (g) females	5.5	5.6	5.6	5.8

Table: Male reproductive parameters

	60 days	100 days
Serum testosterone control	2.21 ± 1.22	5.28 ± 3.30
Serum testosterone 350 ppm	2.58 ± 1.62	**2.65 ± 1.30**
Serum testosterone 1050 ppm	2.38 ± 1.61	**1.72 ± 0.69**
Serum LH control	93 ± 27	128 ± 89
Serum LH 350 ppm	104 ± 34	**99 ± 44**
Serum LH 1050 ppm	82 ± 12	**87 ± 15**
Serum FSH control	555 ± 131	347 ± 57
Serum FSH 350 ppm	539 ± 140	368 ± 175
Serum FSH 1050 ppm	570 ± 112	**525 ± 96**
Epididymal sperm count - control	56 ± 15	132 ± 85
Epididymal sperm count - 350 ppm	44 ± 6	109 ± 42
Epididymal sperm count - 1050 ppm	57 ± 12	110 ± 9

Testosterone: age main effect significant, dose main effect significant
LH: age main effect not significant, dose main effect not significant
FSH: age main effect significant, dose main effect not significant
Epididymal sperm count: age main effect significant, dose main effect not significant

In this study a statistically significant decrease in the number of pregnant females following exposure to 350 ppm of Mn_3O_4 was reported as well as a Mn related maturational delay following exposure to 1050 ppm Mn_3O_4 at day 100 of exposure in male reproductive parameters.

Other observations in experimental animals have reported harmful effects of exposure to manganese on male fertility. A delayed growth and maturation of the testes were reported in young mice dosed orally with 140 mg/kg bw/d of Mn_3O_4 for 90 days (Gray and Laskey, 1980). It was suggested that manganese may directly affect Leydig cells, thus causing a decrease in testosterone secretion (Laskey *et al*., 1985).

The IPCS (1999) report states 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. Studies in animals indicate that manganese can cause direct damage to the testes and late resorptions.

Assessment and comparison with the classification criteria

Effects on sexual function and fertility

For the assessment of effects on sexual function and fertility following exposure to potassium permanganate a one-generation study in rats performed according to OECD TG 415 and GLP was included in the CLH report. Two 28-day repeated dose toxicity studies in rats, one with oral exposure and one with dermal exposure to potassium permanganate were also included by the DS to assess the effects on male and female reproductive organs. No information regarding historical control data for the various parameters measured in the studies was included in the CLH report. Due to limited information on effects on fertility and sexual function following exposure to potassium permanganate, information from other manganese compounds (as requested during public consultation) was also included in the RAC assessment of effects on fertility and sexual function following exposure to potassium permanganate. This information is included in a separate section.

In the one-generation study, Wistar Han rats were exposed to 0, 20, 80 and 320 mg/kg bw/d potassium permanganate by oral gavage (10 males and 25 females/dose group). No mortality was found except for one non-pregnant female in the high dose group that died in the first week after mating. All females in all dose groups were mated, measured as the number of females mated/number of females paired x 100. In the highest dose group some reproductive parameters were affected including a decrease in the fertility index (number of pregnant females/no of females paired x 100; the pregnancy was determined by the presence of spermatozoa in vaginal smears), in dams bearing live pups (gestation index), as well as the number of born pups, see table below. As regards the effect reported on gestation index, it is not clear from the data reported if this effect is related to an effect on fertility or development. No clear effects were reported on the viability and weaning index. The data show a decreased ability of rats to achieve or maintain pregnancy following exposure to potassium permanganate at the highest dose. Limited statistical analysis was included in the CLH report on the reported findings.

Table: Reproduction data

Observation parameters	Dose level (mg/kg bw/d)			
	0	**20**	**80**	**320**
Males/females paired	10/25	10/25	10/25	10/25
Fertility index %*	84	84	80	64
Gestation index %**	90.5	81	85	68.8
Dams with live pups	19	17	17	11
Number of born pups	207	164	163	99
Viability index	98.6	99.4	98.8	96.0
Weaning index	100	100	100	98.0

*number of pregnant females/number of paired females x 100

**number of females bearing live pups/number of pregnant females x 100

Systemic toxicity in males was evident as a decrease in body weight during the 13-week exposure period in the highest dose group reaching a 18.7% decrease (statistically significant) in week 13 of exposure. The decrease in body weight was associated with a decrease in food consumption starting from week 3 and was considered as marked from week 8. The health condition of males was affected in the two highest dose groups, with more pronounced effects in the high dose group including dyspnea, decreased activity, red secretion around nose or eyes, rigidity, piloerection and salivation. In females, no statistically significant changes in body weight were reported before mating, during gestation and lactation in all three dose groups. The food consumption was decreased during the pre-mating period in the high dose group and was associated with a decreased body weight gain. The health condition of females was affected in the high dose with dyspnea in 3 females the 1st week of exposure, in 2 females in the 2nd week, in one animal in the 4th week, and in two animals in the 7th week.

Macroscopic examination showed that all males at the highest dose level showed marked changes in the stomach with blood erosions of mucosa. Microscopic examination in males also showed marked changes in the stomach at this dose level, including erosion, ulceration and inflammation. This is in accordance with the fact that if manganese is in the (VII) oxidation state in potassium permanganate, then ingestion may lead to severe corrosion at the point of contact (ATSDR Report 2012). In the testes a slight damage of spermiogenesis in the high dose group including atrophy of germinal epithelium and atrophy or decreased number of Leydig cells were reported. However, no statistical analysis was included in the CLH report on these findings. Information from other experimental animal studies have also reported harmful effects following exposure to other manganese compounds on male fertility, see separate section on information from other manganese compounds below.

Table: Microscopic findings in males

Observation parameters	Dose level (mg/kg bw/d)			
	0	**20**	**80**	**320**
Testes: insignificant damage of spermiogeneis	1	2	0	0
Testes: slight damage of spermiogeneis	0	0	0	5
Stomach: erosion and ulceration	0	0	1	8
Stomach: inflammation	0	0	1	10

Microscopic examination in females included marked changes in the stomach including erosion, ulceration and inflammation in the highest dose group. Effects were also reported in the female reproductive system including cysts and cellular hyperplasia in the ovaries; and cellular hyperplasia of endometrium, hydrometra and degenerative changes in the uterus. However, the effects in the uterus and ovaries were not dose-related.

In the oral 28-day study male and female Wistar rats were exposed to 0, 40, 100 and 250 mg/kg bw/d potassium permanganate by gavage. Two satellite groups were also included exposed to 0 or 250 mg/kg bw/d of potassium permanganate for 28 days with a recovery period of 14 days. No information was included in the CLH report regarding the statistical significance of the effects reported.

Regarding the general toxicity, a slight decreased body weight in all doses in males and in the high dose females were reported. However, this was associated with decreased food intake. The reduction in body weight was reversible during the recovery period, but not in males in the high dose group. The water intake was also decreased in males and females in the high dose group.

Variations in haematology, biochemistry, and urinalysis were reported, some from 100 mg/kg bw/d. An increase in the relative liver weight was reported in males in all dose groups. Further, an increase in absolute and relative spleen weight in males and females, and in absolute and relative kidney weight in females in the high dose group, was reported.

Microscopic analysis showed effects in the liver and stomach in both sexes. In females eosinophil infiltration and oedema of mucosa was reported in the stomach in the high dose group. However, only sporadic findings in the liver or stomach were reported in males.

As regards effects in the reproductive organs an increase in relative weight of testes and epididymis was reported at 100 and 250 mg/kg bw/d. These effects were not reported in the satellite group. In females an increase in the absolute and relative weight of uterus was reported in all dose groups and in the satellite group.

Histopathological effects in the male and female reproductive organs included no significant effects in testes and epididymis in males nor in the uterus of females.

In the dermal 28-day study, male and female Wistar rats were exposed to 0, 150, 300 and 600 mg/kg bw/d potassium permanganate. The study included two satellite groups exposed to 0 or 600 mg/kg bw/d for 28 days with a recovery period of 14 days. No information was included in the CLH report regarding the statistical significance of the effects reported.

Regarding the general toxicity a slight decrease in body weight and more marked decrease in body weight gain was reported at all doses in both sexes. Some variations in urinanalysis, haematology and biochemistry were reported in both sexes. No statistically significant changes in organ weights were reported. The main histopathological effects included inflammation of skin with parakeratosis or hyperkeratosis in both sexes in the mid- and high dose group.

As regards effects in the reproductive organs, no significant changes were reported in male and female reproductive organ weights and there were no histopathological changes.

Summary

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 foetuses has also been reported in a study where female mice were exposed to manganese chloride, and a reduction in pregnant females in rats were reported 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 have 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.

Comparison with the CLP criteria

Repr. 1A:

There is no information regarding effects on fertility following exposure to humans, so RAC considers that a classification of potassium permanganate as Repr. 1A is not justified.

Repr. 1B:

According to the CLP criteria, classification of a substance in Category 1B is largely based on data from animal studies. Such data should provide clear evidence of an adverse effect on reproductive toxicity in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction should be considered not to be a secondary non-specific consequence of other toxic effects. RAC concludes that the decrease in fertility index, gestation index, dams with live pups and number of born pups observed in the high dose group in the one-generation study occurred together with severe toxic effects and so are considered to be secondary non-specific consequences of parental toxicity, therefore classification of potassium permanganate as Repr. 1B is not justified.

Repr. 2:

According to the CLP criteria classification of a substance in Category 2 is justified when there is some evidence from humans or experimental animal, possibly supplemented with other

information of an adverse effect on sexual function and fertility, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing Category 2 could be the more appropriate classification. RAC 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 consequences 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.

Therefore, **RAC concludes not to classify potassium permanganate for effects on sexual function and fertility**.

Developmental toxicity

For the assessment of developmental toxicity following exposure to potassium permanganate a one-generation study (OECD TG 415 and GLP) and a developmental toxicity study (OECD TG, GLP) was included by the DS. No information regarding historical control data for the various parameters measured was included in the CLH report.

In the one-generation study where Wistar rats were exposed to 0, 20, 80 and 320 mg/kg bw/d potassium permanganate a decreased gestation index was reported at 320 mg/kg bw/d (see relevant table above). This corresponds to a decrease in dams having live pups among the pregnant females. A decrease in the number of viable foetuses was also reported in the study by Elbethieha et al. (2001) following exposure to manganese (II) chloride tetrahydrate (see relevant table above). However, as regards the effect reported on the number of dams having live pups, it is not clear from the data reported if this is related to an effect on fertility or development. Some delay in opening of eyes (until 14 days after birth) was reported at 80 mg/kg bw/d in 2 out of 16 litters and at 320 mg/kg bw/d in 3 out of 10 litters. The delay was not associated with decreased pup body weight. At microscopic examination sporadic pathological findings were reported in the high dose group and included missing testes and epididymis (one pup) one testis reduced (one pup) and stomach mucous membrane congested and chime with blood (two pups). In the brain, an increased absolute and relative weight was reported that reached statistical significance in the high dose level. Vacuolisation in the cortex and/or hippocampus was also more marked in the treated groups compared to the control group (see relevant table above). Manganese has been shown to easily pass through the placenta (Erikson *et al*., 2007) and has been shown to accumulate in greater amounts in the blood and tissues of pregnant laboratory animals (Cawte, 1985) and accumulate in foetal brain after gestational exposure (Kontur and Fetcher, 1988). Further, Donaldson (1987) and Komura and Sakamoto (1992) reported that elevated levels of manganese can be neurotoxic and produce central nervous system damage.

Maternal toxicity in the one-generation study was evident as marked changes in the stomach including erosion, ulceration and inflammation in the high dose group. No statistically significant changes in maternal body weight were reported before mating, during gestation and lactation in all three dose groups.

Table: Effects in the brain in pups

Observation parameters	**Dose level (mg/kg bw/d)**			
	0	**20**	**80**	**320**
Number of examined pups	20	20	20	20
Absolute weight of brain (g)	1.28	1.32	1.30	1.35*
Relative weight of brain (g)	3.34	3.35	3.50	3.68*
Microscopic findings (no. of pups with changes)				
Without changes	17	1	2	2
Vacuolisation of cell nuclei (mild)	3	7	3	2
Vacuolisation of cell nuclei (more marked)	0	12	15	16

*Statistically significant on probability level 0.05 (ANOVA test)

In the developmental toxicity study Wistar rats were exposed to 0, 20, 100 and 500 mg/kg bw/d of potassium permanganate from GD 5 to 19 (Plodíková, 2009). No maternal mortality was reported.

In the high dose group, an increased number of resorptions was reported (implantations without recognisable embryo/foetuses or dead embryo foetuses with external degenerative changes). A dose-depended increase in post-implantation losses (resorptions/implantations x 100) were also reported, however, no statistical analysis was performed on these finding. But when the DS performed a Kruskal Wallis test on the increase in post-implantation losses, statistical significance was reached in the high dose. It should be noted that in the high dose group the post-implantation losses included 8 dams with full litter resorptions which is considered to explain the absence of effects reported on the litter size. At this dose there was also severe toxicity in the maternal animals. A decrease in the number of implantations was also reported in the study by Elbethieha *et al*., 2001 following exposure to manganese (II) chloride tetrahydrate (see relevant table above), however, there was no information regarding whether these were post- or pre-implantation losses. The increased number of resorptions is also considered to be consistent with the decrease in gestation index reported in the one-generation study at 320 mg/kg bw/d. No effect on pre-implantation losses (corpora lutea minus implantations/corpora lutea x 100) were reported in the developmental toxicity study by the DS, see table below. However, in a developmental study performed according to OECD TG 414 with exposure starting on GD 5 pre-implantation losses occurred before the exposure to potassium permanganate started. Therefore, the number of pre-implantation losses reported in the developmental toxicity study is considered to have no impact on the assessment of developmental toxicity since it was induced before the exposure to potassium permanganate started.

Table: Parameters of reproduction in the developmental toxicity study

Observation parameters	**Dose level (mg/kg bw/d)**			
	0	**20**	**100**	**500**
Implantations	9.13	8.95	8.19	8.57
Resorptions	0.61	1.59	1.38	2.83
Corpora Lutea	11.57	12.18	11.24	11.43
Pre- and post-implantation losses (% per female, average)				

Pre-implantation loss[a]	22.84	25.61	28.39	25.49
Post-implantation loss[b]	14.18	22.80	24.65	42.25*
No of foetuses/litter	9.80	9.16	8.41	8.80

*statistically significant with Kruskal Wallis test
[a] intra uterine death, early
[b] intra uterine death, late

A decrease in foetal body weight that reached statistical significance in the highest dose level in female foetuses was reported (3.45, 3.13, 3.12 and 2.78g* at 0, 20, 100 and 500 mg/kg bw/d, respectively).

From the internal examination of variations and malformations a dose dependent increase in skeletal variations was reported for "sternum – decreased no. of ossification sites" and "vertebra, incomplete ossification of cervical vertebrae" both on the foetal and litter level, see table below. The only alterations described as a malformation by the DS was the absence of supraoccipital bone that was seen in one foetus/one litter in the high dose group.

Table: Skeletal alterations (no. of affected foetuses/no. of affected litters)

Alterations	**Dose level (mg/kg bw/d)**			
	0	**20**	**100**	**500**
Total no. of examined foetuses/litters	101/20	91/19	78/17	67/14
Cranium – absence of supraoccipital bone	0/0	0/0	0/0	1/1
Cranium – unossified supraoccipital bone	0/0	1/1	0/0	0/0
Cranium – incomplete ossification of parietal bone	3/2	0/0	8/5	1/1
Cranium - incomplete ossification of frontal bone	0/0	0/0	2/1	0/0
Cranium - incomplete ossification of interparietal bone	1/1	0/0	0/0	0/0
Sternum – decreased no. of ossification sites	40/13 39.6%[a] 65%[b]	49/14 53.8% 73.7%	48/14 61.5% 82.4%	45/12 67.2% 85.7%
Vertebrae - incomplete ossification of cervical vertebrae	0/0 0% [a] 0% [b]	8/2 8.8% 10.5%	8/2 10.3% 11.8%	12/4 17.9% 28.6%
Vertebrae – unossified sacral vertebrae	5/1	18/4	8/2	11/3
Robes – wavy (undulation along the length of a rib)	7/6	3/3	6/4	0/0

[a] Percent of affected foetuses
[b] Percent of affected litters

Maternal toxicity was evident as a statistically significant decrease in body weight during gestation reaching the highest reduction of 14% on GD 8. This was associated with a reduction in food consumption from GD 8 to 14 with more marked reduction in the high dose group. However, the corrected body weight gain (corrected for uterus weight) was only slightly lower (4.3%) compared to the control group. Maternal clinical signs were sporadically reported in the two highest dose groups and included red secreta around nostrils or eyes, piloerection, hoarse breath or dyspnea. In the high dose group cough, gibbous pose, anaemia, apathy and cachexia were also noted. Difficulties with the application of potassium permanganate was also reported in the high dose group and included emesis, return of the test substance into oesophagus and excited behaviour immediately after application of potassium permanganate. No clear correlation could be found between the five dams showing cachexia in the high dose group and the percentages of post-implantation losses.

During necropsy no effects were reported in the control and low dose groups. At 100 mg/kg bw/d erosion of stomach mucosa was reported in 3 females. In the high dose group more frequent occurrence of effects in the stomach were reported (in 18 out of 25 dams) and included erosion, blood in content, ulceration, thickened stomach, oedematous, haemorrhage and congested mucosa.

Summary

In the one-generation study a decrease in gestation index and a slight decrease in viability index was reported at 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. Exposure to other manganese compounds has also shown effects on implantations and the number of viable foetuses. Late opening of eyes from 80 mg/kg bw/d was also reported. In pups it was evident that the main target organ was the brain with increased weight at 320 mg/kg bw/d and marked vacuolisation of cell nuclei (indicating degenerative processes) in the cortex and/or hippocampus in all treated groups with increased severity 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. Decreased number of ossification sites in sternum and incomplete ossification of cervical vertebra was reported in all treated groups. The female pup body weight was also statistically significantly reduced in the high dose group. The maternal toxicity included a statistically significant decrease in body weight, however, only marginal decrease in corrected body weight gain, and several clinical signs and severe microscopic changes in the stomach in the high dose group were observed.

Comparison with the CLP criteria

Repr. 1A:

There is no information regarding effects on fertility following exposure to humans, and thus RAC considers that a classification of potassium permanganate as Repr. 1A is not justified.

Repr. 1B:

According to the CLP criteria, a classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on development is considered not to be a secondary non-specific consequence of other toxic effects. RAC concludes that the main effect could be found in the pups, where the target organ was the brain with an increased weight at 320 mg/kg bw/d and marked vacuolisation of cell nuclei (indicating degenerative processes) in the cortex and/or hippocampus in all treated groups with increased severity with increased doses, i.e., also at doses that did not cause maternal toxicity, indicating severe effects on development following exposure to potassium permanganate. However, due to the limitations of the study (lack of statistical analysis, no historical control) and no available developmental neurotoxicology study, RAC considers that the data is not sufficient to justify a classification in Repr. 1B.

Repr. 2:

According to the CLP criteria, a classification of a substance in Category 2 is justified when there is some evidence from humans or experimental animals, possibly supplemented with other information of an adverse effect on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing Category 2 could be the more appropriate classification.

RAC concludes that the effects reported in the developmental toxicity study on the histopathological changes in pup brain at doses not causing maternal toxicity is considered as some evidence of developmental toxicity and a **classification in Repr. 2 for development is considered justified**.

4.12 Other effects

Not evaluated.

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