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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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	Not evaluated

				Aquatic Chronic 1 – H410	
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

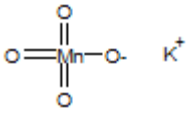
1 IDENTITY OF THE SUBSTANCE

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	HSDB – Toxnet: Association of American Railroads Emergency handling of hazardous materials in surface transportation ;	

	divided the mixture may be explosive Contact with liquid combustible materials may result in spontaneous ignition	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	<u>At 320 mg/kg bw/day</u> - ↓ 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 <u>From 80 mg/kg bw/day</u> - late opening of eyes <u>From 20 mg/kg bw/day</u> - 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	<u>At 500 mg/kg bw/day</u> - ↓ maternal bw - ↑ post-implantation losses - ↓ pup bw <u>From 100 mg/kg bw/day</u> - Erosion of digestive tract in dams <u>From 20 mg/kg bw/day</u> - 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 (+1.4%)	7	14.3	12.5	13.0	14.8
	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

[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 paired	25	25	25	25
Females mated	25	25	25	25
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	1

	0% 	0% 	0% 	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.

4.12 Other effects

Not evaluated.

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