MCL Report for:
Copper Substances

Proposal for mandatory classification and labelling (MCL) based on Annex VI, Part 2 of the retained CLP Regulation (EU) No. 1272/2008 as amended for Great Britain

EC Number: -

CAS Number: -

March 2024

Contents

1 Identity of the substances

1.1 Name and other identifiers of the substances

Table 1: Copper substances considered in this MCL report

Substance name	Index no. (GB MCL list)	EC no.	CAS no.
Copper (I) oxide	029-002-00-X	215-270-7	1317-39-1
Copper (II) hydroxide, copper dihydroxide	029-021-00-3	243-815-9	20427-59-2
Copper (II) carbonate - copper (II) hydroxide (1:1)	029-020-00-8	235-113-6	12069-69-1
Dicopper chloride trihydroxide	029-017-00-1	215-572-9	1332-65-6
Copper thiocyanate	029-015-00-0	214-183-1	1111-67-7
Copper sulphate pentahydrate	029-004-00-0	231-847-6	7758-98-7
Tetracopper hexahydroxide sulphate [1], tetracopper hexahydroxide sulphate hydrate [2]	029-018-00-7	215-582-3	1333-22-8 [1] 12527-76-3 [2]
Bordeaux mixture, reaction products of copper sulphate with calcium dihydroxide	029-022-00-9	-	8011-63-0
Copper flakes (coated with aliphatic acid)	029-019-01-X	**-**	**-**

1.2 Composition of the substance

Not relevant for this report.

2 Proposed mandatory classification and labelling

Table 2: Proposed mandatory acute toxicity estimate (ATE) values according to the GB CLP criteria

Substance Name (GB MCL list)	Index no. (GB MCL List)	EC no.	CAS no.	ATE values
Copper (I) oxide	029-002-00-X	215-270-7	1317-39-1	**Oral: 500 mg/kg bw** **Inhalation: 3.34 mg/L (dusts or mists)**
Copper (II) hydroxide, copper dihydroxide	029-021-00-3	243-815-9	20427-59-2	**Oral: 500 mg/kg bw** **Inhalation: 0.5 mg/L (dusts or mists)#**
Copper (II) carbonate - copper (II) hydroxide (1:1)	029-020-00-8	235-113-6	12069-69-1	**Oral: 500 mg/kg bw** **Inhalation: 1.2 mg/L (dusts or mists)**
Dicopper chloride trihydroxide	029-017-00-1	215-572-9	1332-65-6	**Oral: 299 mg/kg bw** **Inhalation: 2.83 mg/L (dusts or mists)**
Copper sulphate pentahydrate	029-004-00-0	231-847-6	7758-98-7	**Oral: 481 mg/kg bw**
Tetracopper hexahydroxide sulphate; [1]	029-018-00-7	215-582-3	215-582-3 [1]	**Oral: 500 mg/kg bw**

Substance Name (GB MCL list)	**Index no. (GB MCL List)**	**EC no.**	**CAS no.**	**ATE values**
Tetracopper hexahydroxide sulphate hydrate [2]			215-582-3 [2]	
Bordeaux mixture, reaction products of copper sulphate with calcium dihydroxide	029-022-00-9	-	8011-63-0	**Inhalation: 1.97 mg/L (dusts or mists)**
Copper flakes (coated with aliphatic acid)	029-019-01-X	**-**	**-**	**Oral: 500 mg/kg bw** **Inhalation: 0.733 mg/kg bw**

This differs to the ATE proposed in the 17th ATP to EU CLP (i.e., 0.47 mg/L)

3 History of the classification and labelling

The copper substances which are the focus of this MCL report all have entries on the GB MC list, and are all classified for acute toxicity. However, they have not been assigned Acute Toxicity Estimate (ATE) values (See table 3).

Table 3: current entries on the GB MCL list for the 9 copper substances				**Classification**		**Labelling**			**Specific Concentration Limits, M-factors**	**Notes**
Substance Name	**Index No.**	**EC No.**	**CAS No.**	**Hazard Class and Category Code(s)**	**Hazard Statement Code(s)**	**Pictogram, Signal Word Code(s)**	**Hazard Statement Code(s)**	**Suppl. Hazard Statement Code(s)**		
Copper (I) oxide	029-002-00-X	215-270-7	1317-39-1	Acute Tox. 4 Acute Tox. 4 Eye Dam. 1 Aquatic Acute 1 Aquatic Chronic 1	H332 H302 H318 H400 H410	GHS07 GHS05 GHS09 Dgr	H332 H302 H318 H410		M=100	
Copper (II) hydroxide, copper dihydroxide	029-021-00-3	243-815-9	20427-59-2	Acute Tox. 2 Acute Tox. 4 Eye Dam. 1 Aquatic Acute 1 Aquatic Chronic 1	H330 H302 H318 H400 H410	GHS06 GHS05 GHS09 Dgr	H330 H302 H318 H410		M=10	
Copper (II) carbonate - copper (II) hydroxide (1:1)	029-020-00-8	235-113-6	12069-69-1	Acute Tox. 4 Acute Tox. 4 Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H332 H302 H319 H400 H410	GHS07 GHS09 Wng	H332 H302 H319 H410		M=10	

Table 3: current entries on the GB MCL list for the 9 copper substances **Substance Name**	**Index No.**	**EC No.**	**CAS No.**	**Classification**		**Labelling**			**Specific Concentration Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Pictogram, Signal Word Code(s)**	**Hazard Statement Code(s)**	**Suppl. Hazard Statement Code(s)**		
Dicopper chloride trihydroxide	029-017-00-1	215-572-9	1332-65-6	Acute Tox. 4 Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H332 H301 H400 H410	GHS06 GHS09 Dgr	H332 H301 H410		M=10	
Copper sulphate pentahydrate	029-004-00-0	231-847-6	7758-98-7	Acute Tox. 4 Eye Dam. 1 Aquatic Acute 1 Aquatic Chronic 1	H302 H318 H400 H410	GHS07 GHS05 GHS09 Dgr	H302 H318 H410		M=1	
Tetracopper hexahydroxide sulphate; [1] **Tetracopper hexahydroxide sulphate hydrate [2]**	029-018-00-7	215-582-3	215-582-3 [1] 215-582-3 [2]	Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	H302 H400 H410	GHS07 GHS09 Wng	H302 H410		M = 10	

Table 3: current entries on the GB MCL list for the 9 copper substances				**Classification**		**Labelling**			**Specific Concentration Limits, M-factors**	**Notes**
Substance Name	**Index No.**	**EC No.**	**CAS No.**	**Hazard Class and Category Code(s)**	**Hazard Statement Code(s)**	**Pictogram, Signal Word Code(s)**	**Hazard Statement Code(s)**	**Suppl. Hazard Statement Code(s)**		
Bordeaux mixture, reaction products of copper sulphate with calcium dihydroxide	029-022-00-9	-	8011-63-0	Acute Tox. 4 Eye Dam. 1 Aquatic Acute 1 Aquatic Chronic 1	H332 H318 H400 H410	GHS07 GHS05 GHS09 Dgr	H332 H318 H410		M = 10	
Copper flakes (coated with aliphatic acid)	029-019-01-X	-	-	Acute Tox. 3 Acute Tox. 4 Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H331 H302 H319 H400 H410	GHS06 GHS09 Dgr	H331 H302 H319 H410		M=10	

The 17th ATP to EU CLP (Commission Delegated Regulation (EU) 2021/849) introduced ATE values into Annex VI for these copper substances. The following text is copied directly from the 17th ATP:

“Acute Toxicity Estimates (ATE) are mainly used to determine the classification for human health acute toxicity of mixtures containing substances classified for acute toxicity. The inclusion of harmonised ATE values in the entries listed in Annex VI to Regulation (EC) No 1272/2008 facilitates the harmonisation of the classification of mixtures and provides support for enforcement authorities. Following further scientific assessments of some substances, ATE values have been derived by the Agency for dicopper oxide, dicopper chloride trihydroxide, tetracopper hexahydroxide sulphate and tetracopper hexahydroxide sulphate hydrate, copper flakes (coated with aliphatic acid), copper(II) carbonate--copper(II) hydroxide (1:1), copper dihydroxide; copper(II) hydroxide, bordeaux mixture reaction products of copper sulphate with calcium dihydroxide and copper sulphate pentahydrate, in addition to those proposed in the RAC opinions for other substances. Those ATE values should be inserted in the penultimate column of Table 3 of Part 3 of Annex VI to Regulation (EC) No 1272/2008”.

As these ATE values did not originate in opinions of the Committee for Risk Assessment, the Agency is not required to consider them under Article 37 of GB CLP. As such, the Agency has prepared this MCL report according to Article 37A of GB CLP to propose the inclusion of ATE values on the GB MCL list.

4 Justification that action is needed

Acute Toxicity Estimates (ATE) are used to determine the classification of mixtures containing substances classified for acute toxicity. The inclusion of mandatory ATE values in the GB MCL list facilitates the harmonisation of the classification of mixtures and provides support for enforcement activities.

5 Identified uses

Table 4: Identified uses of the copper substances

Substance Name	Index no. (GB MCL list)	EC no.	CAS no.	Use Information (Obtained from the CLH reports for each respective substance (CLH, 2013a-h)
Copper (I) oxide	029-002-00-X	215-270-7	1317-39-1	Copper has been notified under BDP Directive (98/8/EC) as anti-fouling product (product type 21). Copper is intended for use in the protection against fouling of both mobile (including but not limited to marine and freshwater vessels) and stationary (including but not limited to buoys, aquaculture nets and immersed structures) objects. Under PPP Directive (91/414/EC), copper is bacteriostatic and fungistatic in action and is used in the treatment and prevention of bacterial and fungal diseases.
Copper (II) hydroxide, copper dihydroxide	029-021-00-3	243-815-9	20427-59-2	Copper hydroxide had been notified under BPD Directive (98/8/CE) as a wood protective product (product type 08). Under PPP copper hydroxide is bacteriostatic and fungistatic in action and is used in the treatment and prevention of bacterial and fungal diseases.
Copper (II) carbonate - copper (II) hydroxide (1:1)	029-020-00-8	235-113-6	12069-69-1	Copper carbonate has been notified under BPD Directive (98/8/EC) as a wood protective product (product type 08).
Dicopper chloride trihydroxide	029-017-00-1	215-572-9	1332-65-6	Copper is bacteriostatic and fungistatic in action and is used in the treatment and prevention of bacterial and fungal diseases.
Copper thiocyanate	029-015-00-0	214-183-1	1111-67-7	Copper thiocyanate has been notified under BPD Directive (98/8/EC) as an

Substance Name	Index no. (GB MCL list)	EC no.	CAS no.	Use Information (Obtained from the CLH reports for each respective substance (CLH, 2013a-h)
				anti-fouling product (product type 21). Copper is intended for use in the protection against fouling of both mobile (including but not limited to marine and freshwater vessels) and stationary (including but not limited to buoys, aquaculture nets and immersed structures) objects.
Copper sulphate pentahydrate	029-004-00-0	231-847-6	7758-98-7	Copper sulphate pentahydrate has been notified under BPD Directive (98/8/EC) as a disinfectant and general biocidal product (product type 2.05). It is used as a bactericide and incorporated into product used with washing machines, where the presence of copper 2+ ion can exert a biocidal effect.
Bordeaux mixture, reaction products of copper sulphate with calcium dihydroxide	029-022-00-9	-	8011-63-0	Copper is bacteriostatic and fungistatic in action and is used in the treatment and prevention of bacterial and fungal diseases.
Copper flakes (coated with aliphatic acid)	029-019-01-X	**-**	**-**	Coated copper flake has been notified under BPD Directive (98/8/EC) as anti-fouling product (product type 21). Coated copper flake is intended for use in the protection against fouling of both mobile (including but not limited to marine and freshwater vessels) and stationary (including but not limited to buoys, aquaculture nets and immersed structures) objects.
tetracopper hexahydroxide sulphate; [1] tetracopper hexahydroxide sulphate hydrate [2]	029-004-00-0 (Copper sulphate)	215-582-3 [1] 215-582-3 [2]	1333-22-8[1] or 12527-76-3[2]	Tribasic copper sulphate was notified as a PPP under Directive 91/414/EC. It is fungistatic and bacteriostatic in action and is used in the treatment and prevention of fungal and bacterial disease

6 Data sources

This GB MCL proposal was prepared using information submitted during the EU harmonised classification and labelling process (see Section 11 (References) in this report, and documents available at https://echa.europa.eu

7 Physicochemical properties

Not relevant for this MCL report.

8 Evaluation of physical hazards

Not relevant for this MCL report.

9 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not relevant for this MCL report.

10 Evaluation of health hazards

10.1 Acute Toxicity

10.1.1 Human Data

The available human data are applicable to all of the copper substances detailed in this report, therefore the entirety of the available human data is summarised below.

10.1.1.2 Oral Route

Self-poisoning

Although rare in western countries, self-poisoning with copper sulphate has been a common method of suicide in low-income groups in certain areas of India. Chuttani *et al*. (1965) provides an extensive study of 48 cases of copper sulphate self-poisoning including 7 fatalities admitted to one Delhi hospital and 5 further fatalities reported to other Delhi hospitals. Nausea, epigastrial burning and vomiting were the most frequently observed symptoms. Additionally, diarrhoea was reported in 14 patients. Biopsy examination of the fatalities indicated deep erosions in gastric mucosa, haemorrhage in the stomach and small intestine and oedema in the sub mucosa. In 11/48 cases (23%), jaundice (of variable severity) was reported. In the more severe cases, palpable liver enlargement, significantly elevated serum glutamic oxaloacetic transaminase (SGOT, 252.4 ±142 IU) and elevated bilirubin (112 ±8.9 mg/litre) were observed. Centrilobular necrosis and biliary stasis were shown following biopsy examination of liver tissue from fatalities. Post-mortem examination also indicated swollen and congested kidneys with glomerular swelling and necrosis of tubular cells; 13/48 patients (27%) reported anuria and oliguria in 5/48 (10%). Red discolouration of the urine was observed, with haemoglobinuria confirmed in some patients. These findings suggest haemolysis and are consistent with other reports. Haematocrit and serum/plasma appearances were not reported. Serum or blood levels of copper in the cases were elevated 2- or 3-fold compared to normal values. This study provides no reliable data which can be used for human hazard assessment as estimated quantities of ingested copper were based on patients' accounts and are therefore unreliable.

More recent case reports from Mittal (1972) and Jantsch *et al*. (1985) describe massive overdoses of copper sulphate: 175g by a 22 year-old male and 250g by a 42 year-old male. The amounts ingested were considerably higher than the highest estimated dose in Chuttani *et al*. (1965) however both patients survived. This is most likely due to immediate chelation therapy.

Accidental ingestion

Hantson *et al*. (1996) reported the accidental ingestion of 3g of copper sulphate together with an equal amount of zinc sulphate by an 86 year-old female. The patient presented with diarrhoea and vomiting of blue/green material. Gastric lavage, dehydration and chelation therapy with dimercaprol were performed. The patient then suffered hypotension, bronchial inflammation and ulceration and a decline in respiratory function. These symptoms were interpreted as corrosive pneumonitis. Following treatment on a mechanical ventilator for 3 days, the patient made a full recovery. The report considered that the age and patients' health status may have exacerbated their symptoms, however the co-ingestion of zinc sulphate may have also mitigated the symptoms by limiting the uptake of copper.

Therapeutic treatment

Pande and Gupta (1969) reported a 17 year-old male given 1% copper sulphate (2mg/day) orally as a treatment for vitiligo. Systematic effects included renal damage and thrombocytopenic purpura.

10.1.1.3 Inhalation Route

There is limited information available on the acute effects of inhalation of copper-containing materials to humans.

The majority of published studies in humans are focused on metal fume fever (MFF). MFF is a transient illness which appears to develop 4-12 hours after occupational exposure to metal fume and presents as an influenza-like illness with cough and dyspnoea followed by sweating and shivering. Further clinical signs include nausea, headache, weakness, a sweet metallic taste and muscle/joint pain.

Borak *et al*. (2000) extensively reviewed the subject. Based on 7 reports this review aimed to establish whether there is an association between copper and MFF. These reports were identified in a literature search as the only reports that contained original descriptions of copper-exposed workers who developed symptoms consistent with MFF. These 7 reports are summarised below.

Hansen (1911) provided a brief report of MFF-like symptoms in 10 males who worked in a research foundry where scrap copper was melted. The report of this isolated incident contained no qualitative or quantitative data concerning exposure. Borak *et al*. considered that the isolated nature of this incident indicated an association with exposure to contaminants other than copper.

Ten further males who performed hot rolling of copper in a rolling mill reported symptoms of chest discomfort, shivering, nausea and fever in Koelsch *et al*., (1923). The symptoms had not previously been associated with the process and resolved within 24 hours. As with

Hansen (1911), no qualitative or quantitative exposure data were presented. The isolated nature of this incident suggested to Borak *et al*. that contaminants other than copper were involved.

MFF-like syndrome was reported in approximately 50 workers involved in cleaning reactor ovens where pulverised copper was used as a catalyst by Friberg and Thrysin (1947). The heads and faces of the workers were reportedly covered in dust containing mainly cuprous and cupric oxides during their cleaning task. Subsequently these workers suffered symptoms including throat discomfort, burning eyes, nausea and headache, followed by flu-like symptoms, nausea, vomiting, diarrhoea and chest discomfort. These symptoms persisted for more than 72 hours in a number of workers. No quantitative exposure data was provided. The diameter of the dust particles was reported as ranging from 1-15 µm diameter, with more than 70% >5 µm. Borak *et al*. considered that this study did not support an association between copper and MFF, as MFF is usually associated with fine particles (<1 µm diameter) and with less heavy exposure than indicated in this study.

Schiotz (1949) reported 7 workers involved in pulverising cuprous oxide during the production of marine paint who developed symptoms including metallic taste, throat dryness and slight chest oppression, followed by shivering, sweating and fever. These initial symptoms subsided after 20-30 hours. The described working conditions indicated a very high level of exposure, however no quantitative exposure data were provided.

Similar symptoms to the ‘onset of a common cold with chills or warmth, stuffiness of the head, etc.’ were reported in workers exposed to dust generated during polishing of copper plates with aluminium oxide abrasives (Gleason, 1968). Lower respiratory symptoms were not reported, nor were other symptoms characteristic of MFF. A single breathing zone sample of 0.12 mg/m^3 was included although the author of the study suggested that exposure levels may have been ‘2 or 3 times higher’. The symptoms lasted for several weeks, the persistence of these symptoms is not usually associated with MFF, however they did subside following the introduction of ventilation. Borak *et al*. considered that the condition was unlikely to be MFF and that co-exposure to aluminium oxide was also likely.

A single case of a foundry worker who developed an isolated episode of symptoms which included headache, cough, chest pain, chills and shortness of breath following exposure to a molten alloy of copper, beryllium and aluminium, which was poured into a vessel containing alcohol and adhesive glue was described by Hopper (1978). No exposure data were presented. Borak *et al.* noted the co-exposure to other metals which have been implicated in MFF aetiology and the likely exposure to other potentially harmful substances. Consequently, this case-report was not considered as providing evidence of an association between copper and MFF.

Armstrong *et al*. (1983) described a group of 26 workers who suffered MMF symptoms (fever, chills, headache, dyspnoea and nausea) after cutting brass pipes (containing 90%

copper, 10% nickel, and smaller amounts of zinc) with torches in a confined space. A description of the process suggested a high level of exposure, however exposure data for the different metals were not provided. Borak *et al*. considered that co-exposure to other metals implicated in MFF prevented identification of copper as the causative agent.

Borek *et al*. concluded that there was insufficient evidence to conclude whether exposure to copper dust or fume causes MFF as none of the available studies provide adequate exposure data to enable identification of the causative agent(s) of the reported symptoms. Borek *et al*. also noted the lack of any occupational pattern associated with the MFF symptoms.

10.2 Animal Data

10.2.1 Copper (I) oxide

Copper (I) oxide may also be referred to as dicopper oxide or cuprous oxide.

10.2.1.1 Oral Route

Table 5: Summary of animal studies on acute oral toxicity for copper (I) oxide, based on information from CLH (2013a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 401, with deviations GLP	Rat, Sprague-Dawley 5/sex/group	Copper (I) oxide Purity: not stated Vehicle: Arachis oil BP	200, 431, 928 and 2000 mg/kg bw Single gavage dose, 14 days post exposure period	LD_{50} = 1340 mg/kg bw combined	Collier TA, Wilson JC (1984a)
OECD 423, no deviations GLP	Rat, Sprague-Dawley 3/sex/group	Copper (I) oxide Purity: not stated Vehicle: distilled water	200 and 2000 mg/kg bw Single gavage dose, 14 days post exposure period	200 mg/kg bw> LD_{50} >2000 mg/kg bw LD_{50} cut-off >300 mg/kg bw/d	Dirscoll, R. (1999a)
EPA Pesticide assessment guideline, with	Rat, Wistar albino	Copper (I) oxide Purity: not	2500, 5000, 6300 and 7940	LD_{50} = 5400 mg/kg bw	Nitka S. (1991b)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
deviations GLP	5/sex/group	stated Vehicle: Corn oil	mg/kg bw	combined	

Collier TA, Wilson JC (1984)

OECD 401

GLP

Deviations: Yes

1) Information on the test material including the batch no. and the purity were not provided;
2) No justification was given for the choice of vehicle;
3) The lowest limit for the temperature range of the animal room was slightly lower than that recommended in the guideline;
4) Age of animals at study initiation is not indicated.

These deviations are not considered to have influenced the outcome or the integrity of the study.

Method

Copper (I) oxide was administered orally via gavage to fasted Sprague-Dawley rats (5/sex/dose) at doses of 200, 431, 928, and 2000 mg/kg bw. The test material was suspended in arachis oil BP. The animals were observed for death or overt signs of toxicity at 0.5, 1, 2, 3, 4 and 5 hours after dosing, and subsequently once daily for up to 14 days. Individual bodyweights were recorded on days 0, 7 and 14. Surviving animals were killed on day 14. All animals were subjected to a macroscopic post-mortem examination. The LD_{50} and 95% confidence limits were calculated using the Litchfield and Wilcoxon method.

Results

Mortality: 0/10, 0/10, 3/10 and 7/10 animals died at 200, 431, 928, and 2000 mg/kg bw respectively (see table 6 below).

Treatment-related signs were reported at all dose levels, and consisted of lethargy, an abnormal body carriage (haunched posture), piloerection, diarrhoea and a decreased respiratory rate. Further signs of toxicity were reported in rats at some dose levels including ptosis, pallor of the extremities, ataxia and staining around the ano-genital

region. By day 13, survivors showed signs of recovery, judged by external appearance and behaviour.

On day 0 of the study, males weighed 107-216g and females weighed 122-171g. Depressed body weight gains or bodyweight loss was recorded in females at ≥ 431 mg/kg bw and in males at ≥ 928 mg/kg bw during the first week of observation, and in most females during the second week of observation. Bodyweight gains of the remaining rats were within normal limits throughout the two-week observation period.

Autopsy of animals that died revealed pallor of the liver, dark colouration of the kidneys and spleen, gaseous distention of the stomach and ulceration of the glandular region of the stomach and an emptiness and dark staining of the gastro-intestinal tract. Autopsy of surviving animals did not reveal any microscopic abnormalities with the exception of one female in the 928 mg/kg bw dose group, in which an emptiness of the gastro-intestinal tract was observed.

The acute oral LD_{50}s were 1625 (903-2925) mg/kg in males and between 928-2000 mg/kg bw in females. The combined LD_{50} was estimated to be 1340 (918-1956) mg/kg bw.

Table 6: Summary of study findings (Collier and Wilson (1984), reproduced from CLH, 2013)

Dose (mk/kg bw)	Sex	Number dead/number investigated	Time of death (range)	Observations
200	Males	0/5	-	Clinical signs observed shortly after dosing in rats at all levels consisted of piloerection, hunched posture, lethargy, a decreased respiratory rate and diarrhoea. Other signs of toxicity observed in rats at some dose levels included ptosis, pallor of the extremities, ataxia and staining around the ano-genital region. All surviving animals gained bodyweight during the study. Autopsy of animals that died revealed pallor of the liver, dark colouration of the kidneys and spleen, gaseous distention of the stomach and ulceration of the glandular region of the stomach and an
	Females	0/5	-	
431	Males	0/5	-	
	Females	0/5	-	
928	Males	2/5	Day 5	
	Females	1/5	Day 6	
2000	Males	2/5	Day 5-6	
	Females	5/5	Day 5-9	

				emptiness and dark staining of the gastro-intestinal tract
LD_{50} Males and Females: 1340 (918 – 1956) mg/kg bw LD_{50} Males only: 1625 (903 – 2925) mg/kg bw LD_{50} Females only: between 928 and 2000 mg/kg bw				

Driscoll, R. (1999a)

Guideline: OECD 423

GLP: Yes

Deviations: No

Method

Copper (I) oxide was administered as a suspension in distilled water. Groups of three male and three female Sprague-Dawley CD rats were used. Single oral doses of 200 and 2000 mg/kg bw in 10 mL/kg were administered via gavage on day 1. Animals were observed frequently on the day of dosing and then once daily during the 14-day post-dosing period.

Results

No mortalities were observed at 200 mg/kg bw. At 2000 mg/kg bw, all three males died, as well as 2 females. Deaths occurred between day 4-7. A variety of clinical signs were also reported in the 2000 mg/kg bw dose group including hunched posture, piloerection, diarrhoea, lethargy, emaciation, ptosis, decreased respiration rate, laboured respiration, ataxia, pallor of the extremities, dehydration, tiptoe gait and staining around the eyes or snout. Clinical signs occurred on day 2, the surviving female had recovered by day 9. No clinical signs were reported in the 200 mg/kg bw groups. A summary of mortalities is presented in table 7 below.

Surviving animals showed weight gain during the study, but no gross findings were reported. Necropsy of animals that died during the study reported an orange or green coloured material in the digestive tract, haemorrhagic lungs, dark liver, dark kidneys and slight haemorrhage of the gastric mucosa.

Table 7: Mortalities following oral administration of copper (I) oxide to rats (reproduced from CLH, 2013a)

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
200	0/3	-	0/3	-
2000	3/3	Day 4; Day 6; Day 7	2/3	Day 7 (2)

Figures in parenthesis are the number which died on the day specified if more than one.

The acute oral LD_{50} of copper (I) oxide in the rat was estimated to be between 300-500 mg/kg bw.

Nitka S. (1991b)

EPA Pesticide assessment guideline

GLP: Yes

Deviations: Yes

1) Information on the test material including the batch number and the purity were not provided;
2) No justification for the choice of vehicle was provided;
3) The reporting was incomplete (results were not fully discussed).

These deviations are not considered to have influenced the outcome or integrity of the study.

Wistar albino rats (5 male and 5 female) weighing 208-224g, each received a single oral dose of 5000 mg/kg bw/d copper (I) oxide in corn oil. The initial results indicated that the LD_{50} was less than 5000 mg/kg/bw and therefore, further testing was conducted.

Wistar albino rats (5/sex/dose) weighing 208-248g received a single oral dose via gavage of 2500, 5000, 6300 or 7940 mg/kg bw of copper (I) oxide in a gravimetric, corn oil suspension. All animals were observed for pharmacological activity and drug toxicity 1, 3, 6 and 24 hours after treatment and then daily for a total of 14 days. Body weights were recorded at the start of the study, on day 7 and at the end of the study. All animals (survivors and non-survivors) were subjected to gross necropsy after the 14-day

observation period with all findings noted. The LD_{50} was determined by the Litchfield and Wilcoxon method.

0/10, 4/10, 0/10 and 8/10 rats died at 2500, 5000, 6300 and 7940 mg/kg bw, respectively. The most common toxic signs observed were diarrhoea, dehydration and depression, which reversed in animals that survived to 14 days. Hair loss and discolouration of the urine and faeces were also observed.

Gross necropsy findings included: reddening of the small intestines, distended stomach and stomach and intestines filled with dark green fluid. Enlarged kidneys were reported in 1 animal receiving 6300 mg/kg.

The acute oral LD_{50} in the rat (combined male and female) was estimated to be approximately 5400 mg/kg bw.

10.2.1.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Collier and Wilson (1984) and Driscoll (1999a) both reported LD_{50} values between 300 and 2000mg/kg bw, whereas Nitka (1991b) reported a LD_{50} of 5400 mg/kg. The differences in the LD_{50} values may be a result of different particle sizes of the materials tested and/or different vehicles used for administering the test substance.

The estimation of a LD_{50} between 300-500 mg/kg bw by Driscoll (1999a) represents the worst case and meets the criteria for classification.

10.2.1.1.2 Comparison with the GB CLP criteria

The oral LD_{50} for acute oral toxicity lies within the range for classification as Acute Tox.4 (H302: Harmful if swallowed). As no individual study can be selected as the key study for the ATE, the default ATE of 500 mg/kg bw is proposed.

10.2.1.1.3 Conclusion on classification and labelling for acute oral toxicity

Copper (I) oxide meets the criteria for classification in Acute (oral) Toxicity Category 4 (H302: Harmful if swallowed) – this is in agreement with the current MCL list entry. The Agency proposes that an ATE of 500 mg/kg bw is added to the MCL list entry.

10.2.2.2 Dermal route

Not relevant for this MCL report.

10.2.2.3 Inhalation route

Table 8: Summary of animal studies on acute inhalation toxicity (reproduced from CLH, 2013a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
OECD 403 GLP No deviations	Rats Sprague-Dawley 5/sex/group	Copper (I) oxide Purity: not stated (MMAD : 1.92-2.03 µm)	1.28, 2.37 and 5.25 mg/L Nose-only exposure system 4 hour exposure 14 days post exposure	LC_{50} = 2.92 mg/L in males LC_{50} = 3.69 mg/L in females LC_{50} = 3.34 mg/L sexes combined	Blagden, S.M. (2001)
OECD 403 GLP Deviations: Yes	Rat SPF-Wistar 5/sex/group	Copper (I) oxide Mist spray MMAD: no information	Nominal concentration: 30 mg/L Head only exposure 4 hours exposure 14 days post exposure	LC_{50} > 30 mg/l combined	Dickhaus S; Heisler E. (1988a)
OECD 403 GLP Deviations: Yes	Rat Sprague-Dawley 5/sex/group	Copper (I) oxide Dust (MMAD: 4.41-5.10 µm)	Concentration: 3.45-4.43 and 5.09 mg/L (analytical) Nose only exposure 4 hours	LC_{50}= 5.36 mg/l combined	Greenough R J, McDonald P. (1985a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
			exposure 14 days post exposure		
OECD 403 GLP Deviations: Yes	Rat Sprague-Dawley 5/sex	Copper (I) oxide Aerosol MMAD: 4.63 +/- 1.58 µm	Concentration: 5.78 mg/L (analytical) Nose only exposure 4 hours exposure 14 days post exposure	LC_{50} = 5 mg/l combined (approximately)	Greenough R J, McDonald P. (1985b)

Blagden, S.S. (2001)

OECD 403

GLP: Yes

Deviations: None

Method

Groups of 5 males and 5 female Sprague-Dawley rats were exposed to an aerosol atmosphere of copper (I) oxide at gravimetric concentrations of 1.28, 2.37, and 5.25 mg/L for 4 hours via a nose only exposure system. Animals were observed for mortality and reaction to treatment every 60 minutes during exposure, immediately after exposure, one hour after exposure on Day 1 then once daily for 14 days.

The exposure parameters are summarised in table 9 below:

Table 9: Exposure parameters in acute inhalation toxicity study with copper (I) oxide (reproduced from CLH, 2013a).

Parameter	Value		
Nominal concentration (mg/L)	2.58	4.90	12.2
Gravametric concentration (mg/L)	1.28	2.37	5.25
Flow rate (L/min)	15.6	22.5	30.3
Particle size: MMAD (µm) (standard geometric deviation)	2.29 (2.03)	2.58 (1.92)	2.57 (2.00)
Respirable particles < 6 µm (%)	90.2	90.9	88.3

Results

At 1.28 mg/L there was 1 male mortality but no female mortalities. At 2.37 mg/L, 2 males and 1 female died. At 5.25 mg/L, 4 males and 4 females died. All deaths occurred on the day of exposure or within 2 days after exposure. Clinical symptoms during exposure included wet fur, increased, or decreased respiratory rate and laboured respiration, and test material staining of the head. After exposure, similar signs were recorded together with hunched posture, piloerection, pallor of the extremities, ptosis, ataxia, lethargy, gasping or noisy respiration and cyanosis. Surviving animals recovered by Day 10. Mortalities are summarized in table 10, below.

Table 10: Summary of mortalities following administration of copper (I) oxide (reproduced from CLH, 2013).

Gravimetric concentration (mg/L)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
1.28	1/5	Day 2	0/5	-
2.37	2/5	Day 2; Day 3	1/5	Day 2
5.25	4/5	Day 1 (4)	4/5	Day 1; Day 2 (3)

Figures in parenthesis show the number of animals which died on the day specified if more than one.

In the first week after treatment several surviving animals lost weight or showed reduced weight gain, but all gained weight in the second week except for one female exposed to 1.28 mg/L.

At necropsy, the animals which died during the study (or were killed in extremis) showed enlargement and discoloration (pallor, red or dark appearance, dark patches) of the lungs and fluid filled lungs. There were also isolated cases of small intestines, pallor of the liver, pale kidneys, and accentuated lobular pattern on the liver. The majority of surviving animals showed similar lung abnormalities to those of decedents.

The acute inhalation LC_{50} (4-hour) of copper (I) oxide in the rat was 2.92 mg/L for males (with 95% confidence limits of 1.49 to 5.72 mg/L), 3.69 mg/L for females (with 95% confidence limits of 2.24 to 6.08 mg/L) and 3.34 mg/L for males and females combined (with 95% confidence limits of 2.27 to 4.91 mg/L).

Dickhaus S; Heisler E. (1988)

OECD 403

GLP

Deviations: Yes

1) Test material concentrations in the test breathing zone and particle size distribution were not measured;
2) Age and source of test animals were not given;
3) Study methods are generally poorly described.

According to the CLH report, this study report is poorly written however, all efforts have been made to accurately represent the data in this summary.

Method

SPF Wistar rats (3 groups of 5 females and 5 males) were exposed (head-only) for 4 hours to copper (I) oxide powder (60 g/hr) or a 10 or 40% aqueous suspension of copper (I) oxide (60 ml/hr). The air flow was adjusted to 2000 1/h, this gave a nominal concentration of 30 mg/l.

Clinical observations were performed during test material administration, during the 2 hrs post administration, then after 7 and 14 days. Body weights were recorded at the start of the study and after 14 days. All animals were subjected to a macroscopic examination.

Results

There were no deaths. Clinical signs evident during or immediately following exposure included: apathy, sedation, difficult respiration, squat position, reduced reflexes, disturbance of coordination, and tremors.

Group 1 animals (exposed to powder) showed reduced body weight gains. Group 2 and 3 (exposed to aqueous suspension of copper (I) oxide) animals were reported to have shown normal body weight gains. No macroscopic changes were seen in the abdomen or cranial cavity. Examination of lungs of all three groups revealed haemorrhagic infiltrated localisations and multiple red points.

The LC_{50} (4h) of cuprous oxide in the male and female SPF Wistar rat was found to be greater than a nominal concentration of 30 mg/l (the highest achievable concentration). Test material concentrations were not analysed in this study however the highest achievable concentration was administered.

Fulfs JC. (1990)

OECD 403

GLP

Deviations: Yes

1) Particle size distribution was not measured;
2) The purity of the test substance was not reported;
3) Tables of individual clinical signs are not presented;
4) Age of test animal was not given

These deviations are not considered to have influenced the outcome or the integrity of the study.

Method

Sprague-Dawley rats (5 males and 5 females) weighing between 208.8-319.8g, were exposed (nose only) to cuprous oxide for 4 hours. The time weighted average concentration of copper (I) oxide measured in the breathing zone samples was 5.075 mg/l. No information on particle size was available.

All rats were observed at 1, 2 and 4 hours post-dosing and daily thereafter for 14 days. Overt signs of toxicity and/or mortality were noted. Body weights were recorded on study days 0, 1, 7 and 14, and all animals were subjected to a gross necroscopy at the scheduled study termination.

Results

There were no deaths. All animals appeared unkempt at 1-, 2- and 4-hours following exposure. Additionally, 1 male rat appeared unkempt on day 1 and a further male rat appeared unkempt on day 1 and 2 and showed decreased motor activity on day 2. These animals had been confined to the animal holding tube for the period of exposure before

being bathed on removal and therefore, it was difficult to assess if their unkempt nature was due to exposure or handling.

Weight loss was reported in 8/10 animals on the day after treatment, however all animals showed an overall body weight gain at the end of the study. Gross necroscopy at the scheduled termination revealed no abnormal findings.

The acute inhalation LC_{50} (4h) of cuprous oxide in the male and female Sprague-Dawley rat was found to be >5 mg/L.

Greenough R J, McDonald P. (1985a)

OECD 403

GLP

Deviations: Yes

1) No information on test substance purity was given;

2) Procedures for clinical signs observation were inadequately described in the report, and tables of individual clinical signs were not reported;

3) The guideline requires that inhalation equipment should produce 12-15 air changes per hour and oxygen content of 19%. Compliance cannot be confirmed from the test method description in the report.

These deviations are not considered to have influenced the outcome or integrity of the study.

Method

Sprague-Dawley rats (5/sex/concentration) were exposed by nose only to copper (I) oxide for 4 hours in the form of a dust. The mean chamber concentrations of copper (I) oxide measured in breathing zone samples using a gravimetric method were 3.54, 4.43, or 5.09 mg/l. See table 11 below.

Table 11: Analytical concentrations and % respirable particles (reproduced from CLH, 2013a).

Group	Nominal (mg/ml)	Analytical (mg/l)	% respirable particles (<4.7 µm)
1	20.10	5.09	65.1
2	11.53	3.45	52.4
3	12.54	4.43	57.9

All of the rats were observed for clinical signs at frequent intervals throughout the exposure period and for the first hour post-dosing. All surviving animals were observed at least once daily during the subsequent 14-day exposure period. All of the rats were weighed before dosing and on days 2, 3, 4, 7, 10 and 14 post-exposure. All animals that died were subjected to a macroscopic post-mortem examination as soon as possible after death. At the conclusion of the 14-day observation period, all surviving animals were sacrificed and subjected to a macroscopic post-mortem examination as follows:

Each rat was examined prior to opening the abdominal and thoracic cavities. The respiratory tract was subjected to a detailed macroscopic examination for signs of irritancy or local toxicity. All organs were examined *in situ*. The lungs of each animal were removed and weighed to allow calculation of lung-to-body weight ratios. The LC_{50} was determined by the Finney method.

Table 12: The mortality pattern observed in Greenough R J, McDonald P. (1985a) (Based on table in CLH, 2013a)

Group/ Concentration	Deaths	Time of Death	Percentage of animals dying
Group 1 5.09 mg/l	1 male, 1 female	Found dead at 11:00h on Day 1 post exposure.	50%
	1 females	Found dead at 13:30h on Day 1 post exposure.	
	1 male, 1 female	Found dead at 10:00h on Day 2 post exposure.	
Group 2 3.45 mg/l	1 male	Found dead at ca. 11:00 on Day 2 post exposure.	10%
Group 3 4.43 mg/l	1 male	Found dead at ca. 11:00h on Day 1 post exposure.	20%
	1 male	Found dead at ca. 11:00h on Day 2 post exposure	

Results

Animals from all groups showed struggling behaviour and increased urination and defecation during loading into the restraint tubes. Respiratory depression (ca. 40%) was noted for all groups during exposure to cuprous oxide. Following exposure, all animals showed extensive red/brown body staining and exhibited a generally depressed condition.

Respiratory abnormalities were recorded for groups 2 and 3 (3.45 and 4.43 mg/l, respectively).

On day 1 post exposure the surviving animals still tended to show a generally depressed condition, laboured respiration, and red/brown body staining. The persistence of these signs appeared to be dose-related with the surviving animals that were exposed to the highest concentration (5.09 mg/l) showing respiratory abnormalities and red/brown staining for up to 5 and 10 days respectively following exposure. All animals which survived exposure to cuprous oxide exhibited a body weight loss; this weight loss had been re-gained by day 7 of observation, however, the overall weight gain recorded at the end of the 14-day observation period was considered to be reduced.

Gross pathological examination of those animals which died following exposure to cuprous oxide revealed the lungs to have a haemorrhagic appearance. Brown areas were observed in the lungs of several animals, from all dose levels, sacrificed at the end of the 14-day observation period. These brown areas may possibly be due to the accumulation of pigment-laden (haemosiderin) macrophages. However, without histopathological evidence, this cannot be confirmed.

Lung-to-body weight ratios for all animals, especially the females, sacrificed at the end of the 14-day observation period were considered to be slightly elevated. This finding may be attributable to residual pulmonary damage and/or to the lower body weight profile observed.

The LC_{50} (4h) in male and female rats was calculated to be 5.36 mg/l with 95% confidence limits of 4.39-6.54 mg/l.

Greenough R J, McDonald P. (1985b)

OECD 403

GLP

Deviations: Yes

1) No information on test substance purity was given;

2) The age of the test animals was not reported;

3) Procedures for clinical signs observation were inadequately described in the report, and tables of individual clinical signs were not provided;

4) Animal room temperature and humidity during the test procedure showed slightly lower limits than those recommended in the test guideline;

5) The guideline requires that inhalation equipment should produce 12-15 air changes per hour and an oxygen content of 19%. Compliance cannot be confirmed on the basis of the test method description in the report.

These deviations are not considered to have influenced the outcome or the integrity of the study.

Method

Sprague-Dawley rats (1 group of 5 males and 5 females) were exposed (nose only) to an aerosol of cuprous oxide for 4 hours. The mean chamber concentration of cuprous oxide measured in breathing zone samples using gravimetric method was 5.78 mg/l (nominal concentration: 15.02 mg/l). The median diameter of particles was 4.63 (± 1.58) µm.

All of the rats were observed for clinical signs at frequent intervals throughout the exposure period and for the first hour post dosing. All surviving animals were observed at least once daily during the subsequent 14-day post exposure period. Body weights were recorded immediately before dosing and on days 2, 3, 4, 7, 10 and 14 post exposure. Animals were sacrificed at the end of the 14-day observation period and subjected to a macroscopic post-mortem examination as follows:

Each rat was examined prior to opening the abdominal and thoratic cavities. The respiratory tract was subjected to a detailed macroscopic examination for signs of irritancy or local toxicity. All organs were examined *in situ*.

Results

All animals displayed struggling, and increased urination and defecation during loading into the restraint tubes. During exposure to cuprous oxide all animals showed a marked reduction in respiratory rate. All animals appeared subdued and showed piloerection and pronounced/laboured respiration when they were returned to their cages at the end of the exposure period.

On day 1 post exposure 3 males and 3 females were found dead. The surviving animals were in an extremely poor condition, presenting with a subdued/hunched appearance, piloerection, hypothermia, ataxia, pronounced/laboured respiration and red/brown staining on their fur. By day 2 post exposure the condition of the surviving animals (2 males and 2 females) had deteriorated further. Over days 3-4 of the observation period the condition of the animals stabilised, although a blue discolouration was observed around the peri-anal region. On day 4, one of the surviving male animals displayed a prominent, bulbous penis. The animal's movement was impaired and the animal was sacrificed on humane grounds. The penile protrusion was not considered to be directly attributable to exposure to cuprous oxide, although

stress related to the treatment procedures may possibly have been a contributing cause.

By day 5 of the observation period there was a marked improvement in the condition of the surviving animals. However, the animals still appeared subdued, haunched, and showed pronounced respiration and a slightly emaciated and unkempt condition. Animals showed a gradual recovery over days 6-11. No abnormalities were observed during the remainder of the 14-day observation period.

Gross pathological examination of the animals which died following exposure to cuprous oxide revealed the lungs to be grossly enlarged and to have a haemorrhagic appearance. A white frothy fluid was also present in the trachea of 3 of the premature decedents. Those animals that were sacrificed after completion of the 14-day observation period also showed enlarged lungs. Brown areas were also present in the lungs; these were probably due to the accumulation of pigment-laden (haemoriderin) macrophages and were considered to be indicative of previous haemorrhage.

A concentration of 5.78 mg/l of cuprous oxide was considered lethal to rats under the exaggerated exposure regimen used in this study. Sixty percent of the animals died following exposure. One animal was sacrificed on humane grounds (see above). Marked respiratory depression during exposure and the post-mortem observation of pulmonary haemorrhage in the lungs of all animals were attributable to exposure to cuprous oxide.

From the results obtained in this limit test it is considered that the inhalation LC_{50} (4 h) in rats is approximately 5 mg/l.

10.2.1.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

LC_{50} values were derived from two OECD TG compliant acute inhalation studies. Greenough and McDonald (1985a) reported a LC_{50} of 5.36 mg/L and Blagden (2001) reported a LC_{50} of 3.34 mg/L. The difference between these two values may be attributed to the different particle sizes utilised in the studies. The Blagden (2001) study tested copper (I) oxide with mass mean diameter values of 1.92-2.03 µm which were lower than the values used in the Greenough and McDonald (1985a) study (4.41-5.1 µm). Inhalation exposure to smaller particles would be expected to be associated with greater toxicity and therefore a lower LC_{50}. A MMAD between 1 and 4µm with a geometric standard deviation (σg) in the range of 1.5 to 3.0 is recommended by the OECD guideline.

Fulfs (1990) and Dickhaus (1988) both determined LC_{50} values of >5 mg/L. However, no particle size distribution data and no analytical concentration for Dickhaus (1998) were

available, comparison between these two studies with Greenough and McDonald (1985a) and Blagden (2001) is difficult.

The LC_{50} of 3.34 mg/L reported in Blagden (2001) represents the worst case and meets the criteria for classification.

10.2.1.3.2 Comparison with the GB CLP criteria

The LC_{50} of 3.34 mg/L reported by Blagden (2001) represents the lowest available ATE for both sexes combined. This falls within the range for classification as Acute Tox. 4 (H332: Harmful if inhaled) (i.e., $(1 < LC_{50} \leq 5$ mg/L/4 hours), which is in agreement with the classification in the existing MCL list entry.

10.2.1.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Copper (I) oxide meets the criteria for classification in acute inhalation toxicity category 4 (H332: Harmful if inhaled); the Agency proposes that an ATE of 3.34 mg/L (dusts or mists) be added to the MCL list entry.

10.2.2 Copper (II) hydroxide, copper dihydroxide

Copper (II) hydroxide may also be referred to as copper hydroxide or copper dihydroxide.

10.2.2.1 Oral route

Table 13: Summary of animal studies on acute oral toxicity for copper (II) hydroxide, copper dihydroxide, based on information in CLH (2013b)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 401 No GLP No deviations	Rat Wistar 5/sex/dose	Copper hydroxide Purity: 98% Vehicle: deionised water	250-500-1000-1500 mg/kg bw Acute exposure	LD_{50} = 763 mg/kg bw combined	Sterner, W. and Chibanguz a, G. (1988a)
US EPA 81-1 GLP No deviation	Rat Sprague-Dawley 5 or 10 male	Copper hydroxide Purity: not stated	708-1000-1100-1202 and 1413 (♀) and 708-1000-1202-1300 and 1413	LD_{50} = 1280 mg/kg bw males LD_{50} = 1180 mg/kg bw	Deenihan M.J, (1988)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
	and 5 female/dose	Vehicle: deionised water	(♂) mg/kg bw Acute exposure	females	
US EPA 81-1 GLP No deviation	Rat Tac:N(SD)f BR 5/sex/dose	Copper hydroxide Purity: not stated Vehicle: corn oil.	315-795-1260 and 2000 mg/kg bw Acute exposure	LD_{50} = 489 mg/kg bw combined	James, C.N. (1991a)

Sterner, W. and Chibanguza, G. (1988a)

OECD 401

No GLP

Deviations: None

Method

Wistar rats (5/sex/group) were dosed with 500, 1000 and 1500 mg/kg bw of copper hydroxide via gavage. Animals were observed for 14 days following treatment.

Results

Deaths occurred from 1-2 days after treatment. Mortality was observed in 1/5, 3/5, and 4/5 females and in 1/5, 2/5, 1/5 and 5/5 males at 250, 500, 1000 and 1500 mg/kg respectively.

Clinical signs included apathy, slight tremors, spasm or cramps, impaired co-ordination, reduced reflex reaction, cyanosis and pallor of the mucosa, reduced respiratory rate and reduced body temperature. Gross necropsy of decedents revealed residues in the digestive tract and reddening or haemorrhage of the digestive tract mucosa.

Table 14: Summary of LD_{50}s (in mg/kg bw) in males and females reported in Sterner, W. and Chibanguza, G. (1988a) (Reproduced from CLH, 2013b).

	After 24h	After 48h	After 14 days
LD_{50} (male)	989	878	878
LD_{50} (female)	863	863	657
LD_{50} (male+female)	924	819	763

The acute oral LD_{50} (calculated by probit analysis) was 878 mg/kg bw for males (with 95% confidence limits of 582-3025 mg/kg bw), 657 mg/kg bw for females and 763 mg/kg bw for both sexes combined (with 95% confidence limits of 527-1272 mg/kg bw).

Deenihan, M.J. (1988)

US EPA 81-1.

GLP

Deviations: None

Method

Copper hydroxide was administered diluted in deionised water to groups of 5 or 10 male and female Sprague-Dawley rats. Dose levels of 0 (vehicle only; 3 rats/sex), 708, 1000, 1100 (females only), 1202, 1300 (males only) and 1413 mg/kg bw (males and females) were administered by single oral administration via a metal cannula in 10 mL/kg on day 1. Animals were observed daily for the 14-day post-dosing period.

Results

At 708 mg/kg bw, no mortalities were observed. At 1000 mg/kg bw and above mortalities occurred, and the frequency of mortality increased at higher doses up to 100% mortality at 1413 mg/kg bw. The majority of deaths occurred in the first week of dosing. Recorded clinical signs included dehydration, diarrhoea, scruffy coats, and red staining around the snout. Mortalities are summarised in table 15 below.

Table 15: Summary of mortalities reported in Deenihan, M.J. (1988) (Reproduced from CLH, 2013b).

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
0	0/3	-	0/3	-
708	0/5	-	0/5	-
1000	1/5	Day 9	1/5	Day 6
1100	-	-	3/5	Day 2 (3)
1202	3/10	Day 2 (3)	2/5	Day 2; Day 7
1300	4/5	Day 2(3); Day 9	-	-
1413	5/5	Day 1 (4); Day 7	5/5	Day 2 (4); Day 6

Figures in parenthesis are the number which died on the day specified if more than one.

Most surviving animals showed weight gain during the study though some lost weight in the first week after treatment. Findings in surviving animals and those which died during the study included mottled lungs, presence of test material in the digestive tract, pale, mottled liver, discoloured adrenals and haemorrhaging in the digestive tract.

The acute LD_{50} (calculated by Litchfield-Wilcoxon analysis) of copper hydroxide to the rat was 1280 mg/kg bw for males (with 95% confidence limits of 1123-1459 mg/kg bw) and 1180 mg/kg bw for females (with 95% confidence limits of 1054-1322 mg/kg bw).

James, C.N. (1991a)

Us EPA 81-1.

GLP

Deviation: None

Method

Tac:N(SD)f BR rats (5/sex/dose) were administered copper hydroxide as a suspension in corn oil. Dose levels of 315, 795, 1260 and 2000mg/kg bw were administered via gavage in 10mL/kg on day 1. Animals were observed daily for the 14-day post-dosing period.

Results

At 315mg/kg bw there was one male fatality and two female mortalities. At higher doses, the frequency of mortalities increased, all males died at 2000 mg/kg bw, and all females died at 1260 and 2000 mg/kg bw. The majority of deaths occurred by day 2. A summary of mortalities is shown in table 16 below.

Table 16: Summary of mortalities reported in James, C.N. (1991a) (Reproduced from CLH, 2013b)

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
315	1/5	Day 3	2/5	Day 2 (2)
795	4/5	Day 1 (2); Day 2 (2)	3/5	Day 1; Day 2; Day 4
1260	4/5	Day 1 (2); Day 2; Day 7	5/5	Day 1 (3); Day 2; Day 6
2000	5/5	Day 1 (2); Day 2 (2); Day 3	5/5	Day 1 (4); Day 2

Figures in parenthesis are the number which died on the day specified if more than one.

There were a variety of clinical signs recorded including piloerection, decreased activity, diarrhoea, urogenital discharge, laboured breathing and shallow breathing, loose stalls, peri-nasal staining, nasal discharge, prostate habit, unsteady gait, rales, arched back, distended abdomen and hypothermia. The most severe findings occurred within the first few days after administration, although some effects occurred up to day 14. All surviving animals showed weight gain during the study. No gross findings were recorded in surviving animals. The most notable necropsy finding in animals that died during the study was blue/green coloured fluid in the digestive tract and coloured staining of the nose, mouth, anus and urogenital openings.

The acute oral LD_{50} (calculated by probit analysis) of copper hydroxide to the rat was 552 mg/kg bw for males (with 95% confidence limits of 297-1026 mg/kg bw), 451 mg/kg bw for females (with 95% confidence limits of 188-1082 mg/kg bw) and 489 mg/kg bw for the sexes combined (with 95% confidence limits of 312-768 mg/kg bw).

10.2.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Copper hydroxide is of moderate toxicity by the oral route (200< LD_{50} <2000 mg/kg/bw). There was a large range of clinical signs reported following exposure, including but not limited to diarrhoea, piloerection, tremors, impaired co-ordination and impaired respiration.

Generally, no gross necropsy signs were reported in surviving animals however, discoloration or haemorrhage in the digestive tract, effects on liver and/or kidney and the presence of substances similar to the test material in the stomach or intestines was reported in deceased animals.

10.2.2.1.2 Comparison with the GB CLP criteria

The oral LD_{50} lies within the range (300-2000 mg/kg) for classification as Acute Tox.4 (H302: Harmful if swallowed). As no individual study can be selected as the key study for the ATE, the default ATE of 500 mg/kg bw is proposed.

10.2.2.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results of the acute oral toxicity studies, the Agency concludes that copper dihydroxide meets the criteria for classification as Acute Tox.4 (H302: Harmful if swallowed) which is consistent with the existing GB MCL list entry, and proposes an ATE of 500 mg/kg bw.

10.2.2.2 Dermal Route

Not relevant for this MCL report.

10.2.2.3 Inhalation route

Table 17: Summary of animal studies on acute inhalation toxicity (based on information in CLH, 2013b)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
No guideline GLP Deviations	Rat Sprague-Dawley 5/sex	Copper hydroxide Aerosol (MMAD =2.5µm) Purity : 90%	11.65mg/L Whole body exposure 1 hour exposure	LC_{50} >11.65 mg/L combined	Wnorowski, G. (1995)
US EPA 81-3 GLP	Rat Sprague-	Copper hydroxide	0.13-0.30-0.61 and 2.61 mg/L Whole body	LC_{50} male = 0.5 mg/L LC_{50} female =	Rush, R.E. (1992)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
No deviation	Dawley 5/sex/dose	Aerosol (MMAD : 2.9-3.5 µm) Purity : 85.9%	exposure 4 hour exposure	0.61 mg/L LC_{50} = 0.56 mg/L combined	
OECD 403 GLP No deviation	Rat CD/Crl:CD 5/sex/dose	Copper hydroxide Dust MMAD: 2.606-2.828µm Purity: 63.1% (copper)	0.045, 0.205, 1.08, 6.00 mg/L air (analytical concentration) Nose only 4 hours of exposure	$0.205<LC_{50}<1.08$ mg/L	Chevalier, F. (2003)

Wnorowski, G. (1995)

US department of Transport 49 CFR 173.132.

GLP

Deviations: Yes

1) Animals exposed for 1 hour rather than 4 hours;
2) No measurements of actual chamber concentrations taken from breathing zone on three occasions;
3) No continuous measurement of airflow;
4) No record of terminal necropsy.

Method

Sprague-Dawley rats (5/sex) were exposed to an aerosol atmosphere of copper hydroxide at a nominal concentration of 11.65 mg/L (the maximum practical concentration), for 1 hour using a whole-body exposure system. Animals were observed at least daily for 14 days following exposure. The exposure parameters are shown in table 18 below.

Table 18: Summary of exposure parameters in Wnorowski, G. (1995) (Reproduced from CLH, 2013b)

Parameter	Value
Nominal concentration (mg/L)	11.65
Flow rate (L/min)	30
Particle size: MMAD (µm) (standard geometric deviation)	2.5 (2.34)
Respirable particles	96.9

Results

Mortalities are summarised in table 19 below.

Table 19: Summary of mortalities reported following inhalation administration of copper hydroxide in Wnorowski, G. (1995) (Reproduced from CLH, 2013b)

Nominal concentration (mg/L)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
11.65	1/5	Day 2	1/5	Day 1

Clinical symptoms during exposure included ocular and nasal discharge, irregular breathing, dyspnoea, hunched posture and hypoactivity. After exposure, similar signs were recorded together with piloerection. Within a few days, many animals showed reduced food consumption, reduced faecal output and facial staining. All survivors recovered by the end of the observation period. Surviving animals gained weight during the study.

At necropsy, the two animals which died showed discolouration and oedema of the lungs, discolouration of the intestines, mucous filled trachea and rigor mortis.

The acute inhalation LC_{50} (1 hour) was reported to the rat in this study as >11.65 mg/L for males and females. However, this study is unsuitable for classification due to the 1-hour exposure time (rather than 4 hour).

Rush, R.E (1992)

US EPA 81-3

GLP

Deviations: None

Method

Sprague-Dawley rats (5/sex/dose) were exposed to an aerosol atmosphere of copper hydroxide at 0.13, 0.30, 0.61 and 2.61 mg/L (the maximum practical) for 4 hours using a whole-body exposure system. Animals were observed daily for 14 days following exposure. The exposure parameters are summarised in table 20 below:

Table 20: Exposure parameters in Rush, R.E (1992) (Reproduced from CLH, 2013b)

Parameter	**Value**			
Nominal concentration (mg/L)	0.43	0.94	2.97	18.91
Gravimetric concentration (mg/L)	0.13	0.30	0.61	2.61
Flow rate (L/min)	90.6	79.3	61.4	56.6
Particle size: MMAD (µm) (standard geometric deviation)	2.9 (2.3)	3.5 (2.3)	2.3 (2.1)	2.7 (2.2)
Respirable particles <8.7 µm (%)	68.9	64.1	85.9	82.3

Results

At 0.13 and 0.30 mg/L there were no mortalities. At 0.61 mg/L all males and 4 females died. All animals died at 2.61 mg/L. All deaths occurred on the day of exposure. Mortalities are summarised in table 21 below.

The most notable clinical symptoms following exposure were dark material around the face, urine stains, swollen eyelids, lacrimation, salivation, rough haircoat, decreased

activity, breathing abnormalities and decreased defecation. All surviving animals made a complete recovery by the end of the observation period.

One female in the 0.13 mg/L group reported body weight loss in the second week after treatment. In the 0.30 mg/L group, body weight loss and reduced weight gain were recorded in females. Other surviving animals gained weight during the study.

Necropsy of dead animals revealed fluid/mucoid contents in the digestive tract, congested meningeal vessels in the brain and mottled lungs.

Table 21: Summary of mortalities reported following inhalation administration of copper hydroxide in Rush, R.E (1992) (Reproduced from CLH, 2013b).

Gravimetric concentration (mg/L)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
0.13	0/5	-	0/5	-
0.30	0/5	-	0/5	-
0.61	5/5	Day 1	4/5	Day 1
2.61	5/5	Day 1	5/5	Day 1

The acute inhalation LC_{50} (4-hour) of copper hydroxide in the rat was 0.50 mg/L for males (95% confidence interval could not be determined due to lack of partial mortality level), 0.61 mg/L for females (with 95% confidence limits of 0.05 to 1.17 mg/L) and 0.56 mg/L for the sexes combined (with 95% confidence limits of 0.20 to 0.92 mg/L).

Chevalier, F (2003)

OCED 403

GLP

Deviations: None

Method

Rats (5/sex/group) were exposed (nose only) to copper hydroxide for 4 hours at concentrations of 0.045, 0.205, 1.08 and 6 mg/L (analytical concentration) (MMAD: 2.606-2.828 µm). Rats were observed for 14-days post exposure.

In the 6.00 mg/L group, reduced motility and moderate ataxia were reported, along with moderate dyspnoea in 1 male and 1 female. All males and females died immediately after the end of exposure.

At 1.08 mg/L, slight to moderately reduced motility, slight to moderate ataxia, moderately reduced muscle tone and slight dyspnoea were reported. All five males and 3/5 females died prematurely (between the end of exposure and 3 hours after it).

The 0.205 mg/L air group reported lightly reduced motility, slight ataxia and slight dyspnoea. One of 5 males died 3 hours after the end of exposure.

No toxic symptoms or mortality were reported in the 0.045 mg/L group.

The LC_{50} was determined to be $0.205 < LC_{50} < 1.08$ mg/L.

10.2.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

The study by Wnorowski (1995) is not considered relevant as the exposure period was only 1 hour (the classification criteria are based on a 4-hour exposure).

The guideline study by Chevalier (2003) reported a LC_{50} between $0.205 < LC_{50} < 1.08$ mg/L air.

In Rush (1992), the LC_{50} following 4-hour exposure was 0.5 mg/L in males and 0.61 mg/L in females. Necropsy of decedents and some survivors showed lung abnormalities.

10.2.2.3.2 Comparison with the GB CLP criteria

The inhalation LC_{50} lies within the range (0.05-0.5 mg/l) for classification as Acute Tox. 2 (H330: Fatal if inhaled)

10.2.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

The Agency concludes that copper dihydroxide meets the criteria for classification as Acute Tox. 2 (H330: Fatal if inhaled), in agreement with the existing GB MCL list entry, and proposes an ATE of 0.5 mg/L (dusts or mists).

10.2.3 Copper (II) carbonate- copper (II) hydroxide (1:1)

Copper (II) carbonate - copper (II) hydroxide (1:1) may also be referred to as copper carbonate or basic copper carbonate.

10.2.3.1 Oral route

Table 22: Summary of animal studies on acute oral toxicity for copper (II) carbonate-copper (II) hydroxide (1:1) (based on information in CLH, 2013c)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 401 with deviations GLP	Rat Crl:CD(SD)IGS BR 5/sex/group	Copper carbonate Purity: not stated Vehicle: distilled water	Acute exposure 500, 2000 mg/kg bw. 14 days post exposure	LD_{50} between 500 and 2000 mg/kg bw combined	Glaza, S.M. (2001)
No guideline No GLP	Rat Wistar 10/sex/group	Copper carbonate Purity: not stated Vehicle: gum arabic	Acute exposure 764, 917, 1100, 1320, 1584, 1901, 2281 mg/kg bw. 14 days post exposure	LD_{50} = 1350 mg/kg bw (male) LD_{50} = 1495 mg/kg bw (female)	Hasegawa, R. *et al.,* (1989)

Glaza, S.M. (2001)

OECD 401

GLP

Deviations: Yes

1) At test initiation the animals were approximately 8-13 weeks of age (as opposed to 8-12 as specified in the protocol);
2) Only 2 doses were used, not 3.

These deviations are not considered to have impacted the outcome of the study.

Method

Crl:CD(SD)IGS BR rats (5/sex/dose) were administered copper carbonate dry light as a single gavage dose of 500 and 2000 mg/kg bw. There was a 14-day post exposure period to determine clinical observations, bodyweight changes and mortality. Clinical observations were conducted at 1-, 2.5- and 4-hours following test material administration and daily thereafter for 14 days. Mortality checks were conducted twice a day for 13 days after test material administration and again on the morning of day 15.

Bodyweights were determined before test material administration. Additional body weight measurements were taken on day 7 and at either mortality during the post-exposure period or sacrifice at test termination. All animals, whether found dead during the study, sacrificed in a moribund condition or euthanised at test termination, were subject to a macroscopic necropsy examination.

Results

No mortality was reported at 500 mg/kg bw. All 10 animals treated at 2000 mg/kg bw were either found dead (4 males and 5 females) or sacrificed in a moribund condition (1 male) within 7 days of test material administration.

All animals surviving to the end of the observation period exhibited bodyweight gains during the study, with the exception of 1 female which exhibited an loss of 2g during the second week.

The only clinical signs observed in animals treated at 500 mg/kg were non-formed faeces and a dark stained urogenital area. All animals at this dose level returned to a normal appearance by day 9. Clinical signs of toxicity observed in the animals in the 2000 mg/kg bw dose group prior to death or moribund sacrifice included hunched posture, hypoactivity, red stained face, green-tinted/black mucoid/non-formed faeces, few faeces, dark stained urogenital area, cold to touch, dyspnoea and prostration.

The macroscopic necropsy examination conducted at termination of the animals treated at 500 mg/kg bw did not reveal any visible lesions. Test material related legions observed in the 2000 mg/kg bw dose group pertained to abnormally coloured fluid contents in the gastrointestinal tract.

The estimated LD_{50} values were determined to be between 500-2000 mg/kg bw for males, females and both sexes combined.

Hasegawa, R *et al.,* (1989)

No Guideline

No GLP

Method

Wistar rats (10/sex/dose) were administered basic cupric carbonate via a single oral application (gavage) of 764, 917, 1100, 1320, 1584, 1901 and 2281 mg/kg bw. Signs of toxicity were observed for 14 days post-exposure and an anatomical examination was performed after death or at terminal sacrifice. The median lethal dose was determined by Litchfiels and Wilcoxon method.

Results

Mortalities are summarised in table 22 below. Acute toxic symptoms including diarrhoea and haematuria were observed 3-4 days after application. At necropsy, gastric haemorrhage was reported.

The LD_{50} value was calculated to be 1350 mg/kg bw in males and 1495 mg/kg bw in females. Mortality occurred from 1100 mg/kg bw in males (3/10) and females (1/10) (table 23).

Table 23: Acute Oral Toxicity: Mortalities and LD_{50} values reported in Hasegawa, R *et al.,* (1989) (Reproduced from CLH, 2013c).

Mortality [n of 10 animals per group]																LD_{50} (95% confidence limits)
		Days after application														
Sex	Dose (mg/kg)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Male	764															0
	917															0
	1100			2	1											3
	1320		1	1	2											4
	1584		3	3	3											9
	1901		2	4	2	1										9
	2281	1	1	2	2	4										10

1350 mg/kg (1216-1499 mg/kg

	Control															0	
Female	764															0	1495 mg/kg (1298-1734 mg/kg)
	917															0	
	1100					1										1	
	1320				1	3										4	
	1584			1	3	1										5	
	1901	1	1	1	4	2										9	
	2281	1	2	4	2		1									10	
	Control															0	

10.2.3.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

The acute oral LD_{50} in the rat was estimated to be in the range of 500-2000 mg/kg bw for males and females.

10.2.3.1.2 Comparison with the GB CLP criteria

The oral LD_{50} also lies within the range (300-2000 mg/kg) for classification as Acute Tox.4 (H302: Harmful if swallowed). As no individual study can be selected as the key study for the ATE, the converted acute toxicity point estimate of 500 mg/kg bw is proposed.

10.2.3.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results of the acute oral toxicity studies, copper (II) carbonate – copper (II) hydroxide meets the criteria for classification as Acute Tox.4 (H302: harmful if swallowed), which is consistent with the existing GB MCL list entry. As a specific ATE could not be identified, the Agency proposes an ATE of 500 mg/kg bw (converted acute toxicity point estimate; see Table 3.1.2, Annex 1 of GB CLP).

10.2.3.2 Dermal Route

Not relevant for this MCL report.

10.2.3.3 Inhalation route

Table 24: Summary of animal studies on acute inhalation toxicity (Reproduced from CLH, 2013c)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
OECD 403 GLP No deviations	Rat CD/ Crl: CD 5/sex/group	Copper carbonate Purity: 55.1% (copper) Dust (MMAD =8.78-22.887µm)	0.23-1.03 and 5.20 mg/L Nose only 4-hour exposure 14 days post exposure	LC_{50} combined = 1.2 mg/L	Chevalier F. (2004)

Chevalier F. (2004)

OECD 403

GLP

No Deviations

Method

Groups of CD® / Crl: CD® rats (5/sex/group) were exposed via a single (nose only) exposure of 4 hours to a dust atmosphere of copper carbonate at mean achieved atmospheric concentrations of 0.23, 11.03 and 5.20 mg/l.

The percentage of inhalable particles (reported as < 4 µm) was in the range of 36.3 to 45.4 %; the Mean Mass Median Aerodynamic Diameter of particles was in the range of 4.49 to 5.86 µm.

Table 25: Summary of test conditions in Chevalier F. (2004) (Reproduced from CLH, 2013c)

Mean Achieved Atmospheric Concentration (mg/l)	Mean Mass Median Aerodynamic Diameter (µm)	Geometric Standard Deviation
0.23	8.478	2.070
1.03	21.071	2.427
5.20	22.887	2.535

All animals were observed for clinical signs and at the end of the study necropsy was performed.

Results

Slightly reduced motility, slight ataxia and slight dyspnoea were observed at 0.23 mg/L. At 1.03 mg/L, 2 males died within 24h. Clinical signs included moderately reduced motility, slight to moderate ataxia, slight to moderate dyspnoea and slight piloerection. At 5.20 mg/L all animals died prematurely, clinical signs included moderately reduced motility, slight ataxia, slightly reduced muscle tone and moderate dyspnoea.

The LC_{50} for the sexes combined was approximately 1.2 mg/L.

10.2.3.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

One guideline acute inhalation toxicity study was available. The LC_{50} (sexes combined) was approximately 1.2 mg/L.

10.2.3.3.2 Comparison with the GB CLP criteria

A LC_{50} of 1.2 mg/L meets the criteria for classification as Acute Tox 4. (H332: Harmful if inhaled) (i.e., it falls within the range 1 < C < 5 mg/L).

10.2.3.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Copper (II) carbonate- copper (II) hydroxide (1:1) meets the criteria for classification as Acute Tox. 4 (H332: Harmful if inhaled) which is consistent with the exisiting entry on the GB MCL list. The Agency proposes an ATE of 1.2 mg/L (dusts or mists).

10.2.4 Dicopper chloride trihydroxide

Dicopper chloride trihydroxide may also be referred to as copper chloride hydroxide or copper oxychloride.

10.2.4.1 Oral Route

Table 26: Summary of animal studies on acute oral toxicity for dicopper chloride trihydroxide, based on information in CLH (2013d)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 401, no deviations GLP	Rat, Sprague-Dawley 5/sex/group	copper oxychloride Purity: 57.72% copper Vehicle: corn oil	1000, 1400, 1650 and 1950 mg/kg bw Single oral by gavage 14 days post exposure	LD_{50} male >1796 mg/kg bw LD_{50} female >2006 mg/kg bw LD_{50} sexes combined >1862 mg/kg bw	Forster, R (1987a)
OECD 401, no deviations GLP	Rat, Sprague-Dawley 5/sex/group	copper oxychloride Purity: not stated Vehicle: solution of carboxymethyl cellulose	1000, 1400, 1800 and 2200 mg/kg bw Single oral by gavage 14 days post exposure	LD_{50} male = 1083 mg/kg bw LD_{50} female = 1854 mg/kg bw LD_{50} sexes combined >1398 mg/kg bw	Jackson, D. (1994a)
US EPA 81-1, no deviations GLP	Rat, Sprague-Dawley 3, 5 or 10/sex/group	copper oxychloride Purity: not stated Vehicle: deionised water	500, 750, 875, 938 (females only), 1000, 1250 (males only), 1500 and 5000 mg/kg bw Single oral by gavage	LD_{50} males =1200 mg/kg bw LD_{50} female = 950 mg/kg bw	Deenihan, M.J. (1987a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
			14 days post exposure		
OECD 401, no deviations GLP	Mice Hsd:ICR(CD-1) 5/sex/group	copper oxychloride Purity: 57.3% copper Vehicle: coconut oil	200, 400 and 800 mg/kg bw Single administration by gavage 14 days post exposure	LD_{50} males = 221 mg/kg bw LD_{50} sexes combined = 299 mg/kg bw	Haynes, G. (1998).

Forster, R. and Luperi, L. (1987a)

OCED 401

GLP

Deviations: None

Method

Sprague-Dawley CD rats (5/sex/group) were administered copper oxychloride in corn oil. The rats were acclimatised and fasted overnight prior to dosing. Doses (based on a range-finding study) were 1000, 1400, 1650 and 1950 mg/kg bw administered via oral gavage on day 1. Animals were observed daily for the 14-day post-dosing period.

Results

There was 1 female mortality at 1000 and at 1400 mg/kg bw; no male mortalities were recorded at these dose levels. The frequency of mortalities increased at higher doses, 4 males and 2 females died at 1950 mg/kg bw. Mortalities are summarised in table 27 below.

Table 27: Copper oxychloride: mortalities in Forster and Luperi (1987a) following oral administration to rats. (Reproduced from CLH, 2013d)

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
1000	0/5	-	1/5	Day 6
1400	0/5	-	1/5	Day 7
1650	1/5	Day 7	3/5	Day 7 (2); Day 9
1950	4/5	Day 5; Day 7 (3)	2/5	Day 7 (2)

Figures in parenthesis are the number which died on the day specified if more than one.

There was a variety of clinical signs recorded including piloerection, diarrhoea, soiling of the snout, fur, perianal region and urogenital regions, lethargy, hypoactivity, hunched posture, blanching and alopecia. Some of the symptoms became apparent on the day of treatment and others after Day 4 with a number of symptoms persisting up to the end of the study.

A dose-related reduction in body weight gain was reported during the first week of the study. Body weights of surviving animals recovered in the second week. This reduction in body weight is considered to be due more to the varying mortality than to be directly treatment-related. No gross necroscopic findings were reported in surviving animals. The most notable necropsy finding in animals which died during the study was green coloured and/or dark viscous liquid in the digestive tract and dark staining of the urogenital, perianal, perinasal and perioral areas. Enlarged adrenal glands and dark kidneys were also recorded in some animals treated at 1650 or 1950 mg/kg bw.

The acute oral LD_{50} (calculated by probit analysis) of copper oxychloride to the rat was 1796 mg/kg bw for males (with 95% confidence limits of 1645-1947 mg/kg bw), 2006 mg/kg bw for females (with 95% confidence limits of 561-3451 mg/kg bw) and 1862 mg/kg bw for the sexes combined (with 95% confidence limits of 1456-2268 mg/kg bw).

Jackson, D. (1994a)

OECD 401

GLP

Deviations: Yes

Method

Sprague-Dawley rats (5/sex/dose) were administered copper oxychloride in a solution in carboxymethyl cellulose. Doses of 1000, 1400, 1800, and 2200 mg/kg bw administered via oral gavage on day 1. Animals were observed daily for the 14-day post-dosing period.

Results

At 1000 mg/kg bw there were 2 male mortalities but no female mortalities. At higher doses, the frequency of mortality increased, and all males and 3 females died (or were killed *in extremis*) following 1800 and 2200 mg/kg bw. Deaths occurred between day 2 and day 7. A variety of clinical signs were recorded including piloerection, nasal discharge, ataxia, subdued behaviour, diarrhoea, hunched and pale appearance, laboured or slow breathing, swollen abdomen, tail lesions, soiled coats with anal and perigenital staining, ocular discharge, dull/opaque eyes, vocalisation, hypothermia, alopecia and tremors. Most symptoms occurred between Day 2 and 7 though some effects persisted up to Day 15. A summary of mortalities is presented in Table 28 below. Surviving animals showed weight gain during the study.

No gross necropsy findings were recorded in surviving animals. The most notable necropsy finding in animals which died during the study was a green coloured, clear, or dark liquid in the digestive tract. Foci, thickened mucosa and mucoid or liquid contents were also found in the caecum and 1 male treated at 2200 mg/kg bw had pale lungs.

Table 28: Copper oxychloride: mortalities in Jackson (1994a) following oral administration to rats. (Reproduced from CLH, 2013d)

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
1000	2/5	Day 6 (2)	0/5	-
1400	4/5	Day 5 (2) Day 6; Day 7	1/5	Day 6
1800	5/5	Day 3 (2); Day 5; Day 6; Day 7	3/5	Day 3 (2); Day 6
2200	5/5	Day 4 (2); Day 5 (2); Day 6	3/5	Day 2; Day 3; Day 7

Figures in parenthesis are the number which died on the day specified if more than one.

The acute oral LD_{50} (calculated by probit analysis) of copper oxychloride to the rat was 1083 mg/kg bw for males (with 95% confidence limits of 239-1355 mg/kg bw), 1854 mg/kg bw for females (with 95% confidence limits of 1398-4909 mg/kg bw) and 1398 mg/kg bw for the sexes combined (with 95% confidence limits of 1018-1706 mg/kg bw).

Deenihan, M.J. (1987a)

US EPA 81-1

GLP

Deviations: None

Method

Copper oxychloride was administered diluted in deionised water. Groups of 3, 5 or 10 male and female Sprague-Dawley rats were used. Dose levels of 0 (vehicle only), 500, 750, 875, 938 (females only), 1000, 1250 (males only), 1500 and 5000 mg/kg bw were administered by single oral administration via a metal cannula on day 1. Animals were observed daily for the 14-day post-dosing period.

Results

There were no mortalities at doses up to 750 mg/kg bw. At 875 mg/kg bw and above mortalities occurred, and the frequency of mortality generally increased at higher doses up to 100% mortality in both sexes at 1500 mg/kg bw. All deaths occurred in the first week after dosing between day 4 to day 8. Recorded clinical signs include lethargy, diarrhoea and scruffy coats. A summary of mortalities is presented in table 29 below. All surviving animals showed weight gain during the study.

Necropsy examination revealed red mottled lungs in a few surviving animals (1 male at 750 mg/kg, 1 male and 1 female at 875 mg/kg, and 3 females at 1000 mg/kg) but there were no other significant findings. Findings in animals which died during the study included red mottled lungs, gas or fluid (green, black or red in colour) in the digestive tract and peritoneal cavity, discoloured adrenals, small spleens and red staining around the nose and mouth.

Table 29: Copper oxychloride: mortalities in Deenihan (1987a) following oral administration to rats. (Reproduced from CLH, 2013d).

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
0	0/4	-	0/5	-
500	0/3	-	0/3	-
750	0/5	-	0/5	-
875	1/5	Day 5	1/10	Day 5

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
938	-	-	0/5	-
1000	2/5	Day 5; Day 6	4/5	Day 4; Day 6; Day 7; Day 8
1250	1/5	Day 5	-	-
1500	5/5	Day 5 (2); Day 7; Day 8 (2)	5/5	Day 5; Day 4; Day 6; Day 7 (2)
5000	5/5	Day 4 (4); Day 7	5/5	Day 4(4)[a]

Figures in parenthesis are the number which died on the day specified if more than one.

[a]Day of the fifth death not stated in report.

The acute oral LD_{50} (calculated by Litchfield-Wilcoxon analysis) of copper oxychloride to the rat was 1200 mg/kg bw for males (with 95% confidence limits of 1000-1440 mg/kg bw) and 950 mg/kg bw for females (with 95% confidence limits of 864-1045 mg/kg bw).

Haynes, G. (1998)

OECD 401

GLP

Deviations: None

Method

Groups of 5 male and 5 female Hsd:ICR(CD-1) mice were administered copper oxychloride (batch number 19872, containing 57.3% w/w copper, content of copper oxychloride not stated) as a suspension in Alembicol D (fractionated coconut oil). Doses of 200, 400 and 800 mg/kg bw were administered by single oral administration (gavage) of 10 mL/kg on day 1. Animals were observed daily for the 14-day post-dosing period.

Results

At 200 mg/kg bw there was 1 male and 1 female mortality. At 400 mg/kg bw all males and 3 females died, and at 800 mg/kg all males and 4 females died. The deaths occurred between day 1 and day 7. There was a variety of clinical signs recorded including reduced activity, salivation, partly closed eyes, matted fur, staining of skin/fur in the urogenital region, liquid faeces, hunched posture, pallor, lethargy and unconsciousness. Males treated at 400 and 800 mg/kg bw, and females treated at 800 mg/kg bw, produced faeces coloured blue, thought to be unabsorbed test substance. Some of the symptoms became apparent on the day of treatment and others on Day 2 or later. Surviving animals

recovered within the first week after treatment. A summary of mortalities is presented in table 30 below. All surviving animals showed expected weight gain during the study.

No gross necropsy findings were recorded in surviving animals. The most notable necropsy finding in animals that died during the study was green coloured material in the digestive tract. Staining of the skin/fur particularly the urogenital areas was also recorded in most animals.

Table 30: Copper oxychloride: mortalities in Haynes, G. (1998). following oral administration to mice. (Reproduced from CLH, 2013d).

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
200	1/5	Day 3	1/5	Day 2
400	5/5	Day 3; Day 4; Day 5 (2); Day 7	3/5	Day 2; Day 3 (2)
800	5/5	Day 1; Day 2 (3); Day 3	4/5	Day 1; Day 2; Day 4 (2)

Figures in parenthesis are the number which died on the day specified if more than one.

The acute LD_{50} (calculated by probit analysis) of copper oxychloride was 229 mg/kg for the sexes combined (with 95% confidence limits of 215-414 mg/kg bw).

10.2.4.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

The majority of the available studies reported LD_{50} values between 200 and 2000 mg/kg bw. LD_{50} values were >300 mg/kg bw in rats. Haynes (1998) reported a combined LD_{50} of 299 mg/kg bw in mice (221 mg/kg bw in male mice).

10.2.4.1.2 Comparison with the GB CLP criteria

The available acute oral toxicity studies report a range of LD_{50}s between 221-2006 mg/kg in rats and mice. The lowest LD_{50} values were reported in mice – the LD_{50} reported by Haynes (1998) (299 mg/kg bw for male and female mice combined) meets the criteria for classification as Acute Tox 3. H301: Harmful if swallowed.

10.2.4.1.3 Conclusion on classification and labelling for acute oral toxicity

Dicopper chloride trihydroxide meets the criteria for classification as Acute Tox. 3; H301 (Harmful if swallowed) which is consistent with the existing GB MCL list entry. The Agency proposes an ATE of 299 mg/kg bw.

10.2.4.2 Dermal Route

Not relevant for this MCL report.

10.2.4.3 Inhalation route

Table 31: Summary of animal studies on acute inhalation toxicity (Reproduced from CLH, 2013d).

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
US Department of Transport 49 CFR 173.132. with deviations GLP	Rat HSD:SD 5/sex/group	copper oxychloride Purity: not stated (MMAD =2.8µm)	11.4 mg/L Whole body exposure system 1-hour exposure 16 days post exposure	LC_{50} >11.4 mg/L	Holbert, M.S. (1993)
OECD 403 GLP	Rat Crl:CD(SD) IGS BR 5/sex/dose	copper oxychloride Purity: 57.28% copper (MMAD: 2.9-3.5 µm)	1.14, 1.79 and 2.77 mg/L Nose-only exposure system 4-hour exposure 14 days post exposure	LC_{50} = 2.83 (mg/L) in males LC_{50} > 2.77 mg/L in females	Wesson, C.M. (2003)

Holbert, M.S. (1993)

US Department of Transport 49 CFR 173.132.

GLP

Deviations: Yes.

1) Animals exposed for 1 hour rather than 4 hours.

Method

Rats (5 male and 5 female) were exposed to an aerosol atmosphere of copper oxychloride at 11.4 mg/L (maximum practical concentration, time weighted average gravimetric concentration) for 1 hour using a whole-body exposure system. Animals were observed at least once daily for 16 days following exposure.

Table 32: Copper oxychloride: exposure parameters in Holbert (1993) (Reproduced from CLH, 2013d)

Parameter	Value
Nominal concentration (mg/L)	70.3
Gravimetric concentration (mg/L)	11.4
Flow rate (L/min)	109
Particle size: MMAD (µm) (standard geometric deviation)	2.801 (2.459)
Respirable particles < 9 µm (%)	86.9

Results

One male and two females died. All deaths occurred 5 or 6 days after exposure. Clinical symptoms after exposure included decreased activity, diarrhoea, lacrimation, nasal discharge, piloerection, polyuria and ptosis. All survivors recovered from these signs by the end of the observation period.

Table 33: Copper oxychloride: summary of mortalities in Holbert (1993) following inhalation administration (Reproduced from CLH, 2013d)

Gravimetric concentration (mg/L)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
11.4	1/5	Day 7	2/5	Day 6; Day 7

Body weight loss was recorded in 3 surviving males and 3 surviving females in the first week after treatment, but these animals gained weight thereafter.

At necropsy, discoloured and swollen lungs, discoloured mucous in the abdominal cavity, discoloured contents in the intestinal tract and gas in stomach were recorded in animals which died during the study. Pale and mottled lungs were recorded in surviving animals.

The acute inhalation LC_{50} (1-hour) of copper oxychloride to the rat was > 11.4 mg/L for males and females. This study is not suitable for classification as the exposure time was 1-hour rather than 4-hours.

Wesson, C.M. (2003)

OECD 403

GLP

Deviations: None

Method

Crl:CD (SD) IGS BR rats (groups of 5 males and 5 females) were exposed to an aerosol atmosphere of the test substance at 1.14, 1.79 and 2.77 mg/L for 4 hours using a nose-only exposure system. Animals were observed for clinical signs at least once daily for 14 days following exposure.

Table 34: Copper oxychloride technical: exposure parameters in Wesson (2003) (Reproduced from CLH, 2013d)

Parameter	Value		
Nominal concentration (mg/L)	8.22	10.9	12.5
Measured concentration (mg/L)	1.14	1.79	2.77
Flow rate (L/min.)	50	60	60
Particle size: MMAD (standard geometric deviation)	3.23 (1.97)	3.55 (2.03)	3.65 (2.13)
Respirable particles < 4 μm (%)	62.5	56.7	54.9

Results

There were no deaths at 1.14 mg/L. At 1.79 mg/L, one female and two males died overnight following exposure. At 2.77 mg/L, two males died overnight following exposure. During exposure, clinical signs included increased respiration rate, laboured and/or noisy respiration. After exposure, all surviving animals showed wet fur, hunched posture, piloerection and fur staining by the test material. These signs were considered to be

associated with the restraint procedure, and in isolation were not indicative of toxicity. One hour post exposure, animals at 1.79 and 2.77 mg/L showed increased or decreased respiratory rate, laboured and/or noisy respiration, lethargy, ataxia and tiptoe gait. Ptosis, pallor of extremities and hypothermia were observed in some males at 1.17mm. On the day following exposure, clinical signs included increased respiratory rate, noisy and/or laboured respiration, hunched posture, pilo-erection and occasional instances of red-brown staining of the snout. One female at 1.79 mg/L showed tiptoe gait on day 2. Some females at 2.77 mg/L also showed ataxia, tiptoe gait, red brown staining around eyes and closed eyes. All survivors showed normal clinical signs by days 7 (at 1.14 mg/L) or days 8 or 9 after exposure.

Table 35: Copper oxychloride technical: summary of mortalities in Wesson (2003) following inhalation exposure (Reproduced from CLH, 2013d)

Males			Females		
Measured dose (mg/L)	Mortality	Time of death	Measured dose (mg/L)	Mortality	Time of death
1.14	0/5	-	1.14	0/5	-
1.79	2/5	Day 2	1.79	1/5	Day 2
2.77	2/5	Day 2	2.77	0/5	-

All fatalities occurred overnight after exposure.

There was a reduction in body weight or a reduction in body weight gain in the first week after exposure. Normal body weight gain was recorded in the second week.

During necropsy lung abnormalities were recorded in animals that died during the study. Several of the surviving animals also showed lung abnormalities at terminal kill.

The acute inhalation LC_{50} (4-hour) of copper oxychloride technical TO was 2.83mg/L in males (with 95% confidence limits of 2.23-7.22mg/L) and > 2.77 mg/L in females. The LC_{50} for the combined sexes was 4.74 mg/L (with 95% confidence limits of 3.09-384 mg/L).

10.2.4.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

The LC_{50} reported in Holbert (1993) (>11.4 mg/L) cannot be used for classification purposes as the exposure period was only 1 hour, whereas the classification criteria are based on a 4-hour exposure period.

A guideline-compliant study (Wesson, 2003) reported a LC_{50} of 2.83 mg/L in male rats (the most sensitive sex).

10.2.4.3.2 Comparison with the GB CLP criteria

The LC_{50} of 2.83 mg/L lies within the range for classification as Acute Tox. 4 (H332: Harmful if inhaled) (i.e., 1 < C ≤ 5.0 mg/L).

10.2.4.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Dicopper chloride trihydroxide meets the criteria for classification as Acute Tox. 4 (H332: Harmful if inhaled), which is consistent with the existing MCL list entry. The Agency proposes an ATE of 2.83 mg/L (dusts or mists).

10.2.5 Copper sulphate pentahydrate

10.2.5.1 Oral Route

Table 36: Summary of animal studies on acute oral toxicity for copper sulphate pentahydrate, based on information in CLH (2013e)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 401 GLP	Rat Sprague Dawley 5/sex/dose	Copper sulphate pentahydrate Purity: 99-100.5% Vehicle: purified water	447-562-708 and 893 mg/kg bw Acute exposure 14 days post exposure	LD_{50} = 481-482 mg/kg bw combined	Lheritier, M. (1994)
OECD 401 GLP	Rat Sprague Dawley 5/sex/dose	Copper sulphate pentahydrate Purity: 25.4% (copper) equivalent to 99.9% of copper sulphate pentahydrate. Vehicle: purified	500-1000-2000 mg/kg bw Acute exposure 14 days post exposure	LD_{50} = 666 mg/kg bw female	Manciaux, X. (1998)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
		water			

Lheritier, M. (1994)

OECD 401

GLP

Deviations: None

Method

Sprague Dawley rats (5/sex/dose) were administered doses of 447, 562, 708, and 893 mg/kg by oral gavage of copper II pentahydrate solution. Clinical signs and body weights were observed over 14 days post-dose and all animals were subjected to necropsy.

Results

Mortalities in the 447, 562, 708 and 893 mg/kg treatment groups were 40, 70, 90 and 100% respectively (see table 37 below). Mortalities occurred within the first 4 hours after dosing. Weight loss of 11-15% of the fasted body weight occurred in male and female rats at all dose levels within 1 day following dosing. The majority of surviving rats gained weight during the second week of observation.

Table 37: Mortality and mean body weight in Lheritier (1994) (Reproduced from CLH, 2013e)

Group	Dose Level (mg/kg)	Mean bodyweight (g)			% mortality
		Day 1[1]	Day 8	Day 15	
Male	0	176.6	243.8	298.4	0
Female		148.2	180.8	198.8	0
Male	447	184.4	219.7	278.3	40
Female		148.8	168.3	201.7	40
Male	562	176.8	225.0	284.7	40
Female		149.2	NA	NA	100
Male	708	176.8	NA	NA	80
Female		148.4	NA	NA	100
Male	893	179.0	NA	NA	100
Female		148.4	NA	NA	100
LD_{50} value	Bliss' method = 482 mg/kg bw				

	Litchfield & Wilcoxon's method = 481 mg/kg bw
[1] = Fasted body weight NA- Not applicable, all rats dead	

Clinical signs observed included lethargy, prostrate posture, green coloured diarrhoea, voiding few faeces and moribundity. Stomach distention with green fluid occurred in 1 female dosed at 562 and 1 male dosed at 708 mg/kg and 1 female at 447 mg/kg (this female also had liver discolouration). The intestines of 2 males at 893 mg/kg and 1 male at 447 mg/kg were slightly congested. There were no other macroscopically detectable abnormalities.

LD_{50} (male and female rats combined): 482 mg/kg (95% confidence limits of 403 to 575 mg/kg) by Bliss method 481 mg/kg (95% confidence limits of 400 to 580 mg/kg) by Litchfield & Wilcoxon's method.

Manciaux, X. (1998)

OECD 401

GLP

Deviations: None

Method

Sprague-Dawley rats (5/sex/dose) were administered copper sulphate pentahydrate (batch number 1/255/97, containing 25.4% w/w copper, content of copper sulphate pentahydrate not stated but approx. equivalent to 99.9%) in purified water. Doses (based on range-finding study) of 500, 1000, and 2000 mg/kg bw were administered by single oral administration by metal cannula. Animals were observed frequently on the day of dosing and then once daily for the 14-day post-dosing period. Decedents and animals surviving to 14 days were subject to gross necropsy.

Results

At 2000 mg/kg bw 5 male mortalities occurred. No male mortalities occurred at lower doses. In females, there were 2 deaths at 500 mg/kg bw, 3 deaths at 1000 mg/kg bw and 5 deaths at 2000 mg/kg bw. All deaths occurred on day 1 or 2. There were a variety of clinical signs recorded including sedation, hypoactivity, piloerection, dyspnoea, tonic-clonic convulsions and lateral incumbency. Symptoms appeared 30 minutes after administration and persisted in some surviving animals until day 2. A summary of mortalities is presented in table 38 below. All surviving animals showed expected weight gain during the study. No

gross findings were recorded in surviving animals. In almost all animals that died during the study, a blue colouration of the stomach was observed.

Table 38: Mortalities in Manciaux (1998) following oral administration of copper sulphate pentahydrate to rats (Reproduced from CLH, 2013e)

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
500	0/5	-	2/5	Day 2 (2)
1000	0/5	-	3/5	Day 1 (3)
2000	5/5	Day 1 (5)	5/5	Day 1 (5)

Figures in parenthesis are the number which died on the day specified if more than one.

The acute oral LD_{50} (calculated by probit analysis) of copper sulphate pentahydrate to the rat was 666 mg/kg bw for females (with 95 % confidence limits of 0 to 1308 mg/kg bw).

Short summary and overall relevance of the provided information on acute oral toxicity

Two guideline studies in Sprague Dawley rats are available for copper sulphate pentahydrate. The range of clinical signs following exposure included: diarrhoea, piloerection, ataxia, lethargy, hunched posture, sedation, hypoactivity, dyspnoea, tonic-clonic convulsions and impaired respiration. Surviving animals generally showed no gross findings at necropsy, but animals which died during the studies showed discoloration or haemorrhage in the digestive tract, effects on liver and/or kidney and the presence of substances similar to the test material in the stomach or intestines.

Comparison with the GB CLP criteria

The reported LD_{50} values were all in the range $300 < LD_{50} \leq 2000$ mg/kg bw, which supports classification as Acute Tox.4 (H302: Harmful if swallowed). The lowest LD_{50} value reported was 481 mg/kg bw (male and female rats combined), so this value is selected as the ATE.

10.2.5.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results of the acute oral toxicity studies, copper sulphate pentahydrate meets the criteria for classification as Acute Tox.4 (H302: Harmful if swallowed), which is consistent with the existing GB MCL list entry. The Agency proposes an ATE of 481 mg/kg bw.

10.2.5.2 Dermal Route

Not relevant for this MCL report.

10.2.5.3 Inhalation Route

Not relevant for this MCL report.

10.2.6 Bordeaux mixture, reaction products of copper sulphate with calcium dihydroxide

10.2.6.1 Oral Route

Not relevant for this MCL report.

10.2.6.2 Dermal Route

Not relevant for this MCL report.

10.2.6.3 Inhalation Route

Table 39: Summary of animal studies on acute inhalation toxicity for Bordeaux mixture, based on information in CLH (2013f)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 403 GLP Purity: not stated	Rat, Sprague-Dawley 5/sex	Nominal concentration= 2.67; 5.42 and 8.65mg/L (MMAD=1.75-2.2-2.15µm)	Whole body exposure 4-hour exposure 14 days post exposure Acute inhalation	LC_{50} (4-hour): 1.97 mg/L (♂) LC_{50} (4-hour): > 2.02 mg/L (♀)	Merkel, D.J. (2001)
OECD 403 GLP Purity: 26.5% (w/w copper)	Rat, Sprague-Dawley 5/sex/group	Nominal concentration = 1.10; 1.96 and 4.88 mg/L (MMAD= 3.83; 3.27; 3.53µm)	Nose-only 4 hours of exposure 14 days post exposure Acute inhalation	LC_{50} (4-hour): 3.98 mg/L (♂) LC_{50} (4-hour): > 4.88 mg/L (♀)	Anderson, B.T. and Stewart, D. (2002)

Merkel, D.J. (2001)

OECD 401

GLP

Deviations: No

Method

Groups of animals were exposed to an aerosol atmosphere of the test substance at gravimetric concentrations of 1.05 mg/L (5 males), 2.02 mg/L (5 males and 5 females) and 3.08 mg/L (5 females, maximum practical concentration) for 4 hours using a whole-body exposure system. Animals were observed for mortality and reaction to treatment at least every 30 minutes during exposure (1.05 and 2.02 mg/L treatments) or for the first hour of exposure (3.08 mg/L treatment) on Day 1 until accumulation of the test substance on the walls of the exposure chamber prevented this. After exposure, animals were observed at least once daily for 14 days. Body weights were recorded prior to exposure and after 7 days (Day 8), and 14 days (Day 15) or at death. Gross pathological examinations were performed on decedents and animals surviving for 14 days. The exposure parameters are summarised in table 40 below.

Table 40: Bordeaux Mixture: exposure parameters in Merkel (2001) (Reproduced from CLH, 2013f).

Parameter	Value		
Nominal concentration (mg/L)	2.67	5.42	8.65
Gravimetric concentration (mg/L)	1.05	2.02	3.08
Flow rate (L/min.)	50.6	50.7	50.6
Particle size: MMAD (µm) (Standard geometric deviation)	1.75 (2.24)	2.250 (2.22)	2.25 (2.15)
Respirable particles < 9µm (%)	98.5	96.4	97.4

Results

There were no mortalities at 1.05mg/L. At 2.02 mg/L, 3 males died with no female mortalities. At 3.08 mg/L, all males died. All deaths occurred on the of exposure or within 1 day following exposure. Clinical symptoms during exposure included ocular and nasal discharge, irregular breathing, dyspnoea, hunched posture and hypoactivity. After exposure, similar signs were recorded together with facial staining and/or reduced faecal volume. Surviving animals recovered by Day 5. Mortalities are summarised in Table 41 below.

Table 41: Bordeaux mixture: summary of mortalities in Merkel (2001) following inhalation administration (Reproduced from CLH, 2013f).

Gravimetric concentration (mg/L)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
1.05	0/5	-	-	-
2.02	3/5	Day 1 (2), Day 2	0/5	-
3.08	5/5	Day 1 (4), Day 2	-	-

Figures in parenthesis are the number which died on the day specified if more than one.

At 2.02 mg/L, two females lost weight in the first week after treatment however they gained weight in the second week. Other surviving animals gained weight during the study. At necropsy, the animal which died during the study showed rigor mortis, oedema of the lungs, discolouration of the liver, discolouration of the lungs and mucous filled trachea. Surviving animals showed no gross abnormalities.

The acute inhalation LC_{50} (4-hour) of Bordeaux Mixture to the rat was 1.97 mg/L for males (with 95% confidence limits of 1.63-2.47 mg/L) and > 2.02 mg/L for females.

Anderson, B.T. and Stewart, D. (2002)

OECD 403 (1981)

GLP

Devaitions: No

Method

Sprague-Dawley rats (5/sex/dose) were exposed to an aerosol atmosphere of Bordeaux Mixture technical (batch number 01216-1, containing 265.2g copper/kg) at 1.10, 1.96 and 4.88 mg/L for four hours using a nose-only exposure system. The three exposures used were performed on the same batch of animals. Animals exposed to 1.96 mg/L were 8-9 weeks of age, 225-265 g (males) and 174-192 g (females), animals exposed to 4.88 mg/L were 9-10 weeks of age, 258-276 g (males) and 188-210 g (females) and animals exposed to 1.10 mg/L were 10-11 weeks of age, 291-310 g (males) and 168-214 g (females). Animals were observed for reaction to treatment continuously during exposure and clinical signs recorded every 30 minutes. Animals were observed immediately after exposure, 1 to 2 hours after exposure (Day 1), then daily for 14 days following exposure. Body weights were recorded prior to treatment and after 2, 4, 7, 10 and 14 days (Days 3, 5, 8, 11 and 15). Gross pathological examinations were performed on decedents and animals surviving for 14 days. The respiratory tract of all animals was subjected to detailed macroscopic examination. The lungs of all animals were weighed and lung:body weight ratios calculated. The exposure parameters are summarised in Table 42.

Table 42: Bordeaux Mixture technical: exposure parameters in Merkel (2001) (Reproduced from CLH, 2013f).

Parameter	Value		
Nominal concentration (mg/L)	1.10	1.96	4.88
Measured concentration (mg/L)	4.3	10.9	25.0
Flow rate (L/min)	20	20	20
Particle size: MMAD (standard geometric deviation)	3.83 (2.042)	3.27 (2.044)	3.35 (2.178)
Respirable particles < 4.4 μm (%)	53.1	46.8	47.4

Results

No females died during the study. At 1.10 mg/L there were no deaths in males. At 1.96 mg/L, 1 male died on day 1 after dosing and at 4.88 mg/L 2 males died on day 1 after dosing and on day 2 after dosing, 1 further male died. Slow and laboured respiration were

observed during exposure. After exposure, surviving animals had test compound on their heads and showed laboured respiration, pale, unkempt appearance, subdued behaviour, pallor, intermittent body tremors, hunched posture, unsteady on feet and two animals were recorded as having one eye closed in the post exposure period. All effects were reversible in surviving animals by day 1 for the 1.10 mg/L, day 2 for the 1.96 mg/L and day 5 for the 4.88 mg/L groups respectively. Mortalities are summarised in table 43 below.

Table 43: Bordeaux mixture: summary of mortalities in in Merkel (2001) following inhalation exposure (reproduced from CLH, 2013f).

Males			Females		
Dose (mg/L)	Mortality	Time of death	Dose (mg/L)	Mortality	Time of death
1.10	0/5	-	1.10	0/5	-
1.96	1/5	Day 1	1.96	0/5	-
4.88	3/5	Day 1 (2) Day 2 (1)	4.88	0/5	-

Figures in parenthesis are numbers that died on the specified day, if more than one.

Body weight: Surviving animals at 4.88 mg/L showed body weight loss after exposure but had recovered to day 0 values between days 4 and 7 of the observation period. There was an initial body weight loss in the animals treated at 1.10 and 1.96 mg/L. Normal body weight gain was recorded in all animals by the end of the observation period.

Necropsy: The 3 males found dead at 4.88 mg/L were in an autolysed condition; 2 of these animals had spongy and dark lungs, the third had spongy and mottled lungs. The lungs of the single male killed on day 1 at 1.96 mg/L were noted as mottled and spongy, and 1 male in this group showed red foci on all lung lobes at scheduled terminal kill. There were no other abnormalities.

Lung:body weight: There was no effect on the lung:body weight ratio in surviving animals. In animals that died during the study, lung weights were increased, and lung: body weight ratios were increased.

For the sexes combined, the acute inhalation LC_{50} (4 hour) was >4.88mg/L. However, as there were no deaths in females, the LC_{50} must be calculated using only the male data. The LC_{50} (4-hour) for males was 3.98 mg/L (with 95% confidence limits of 1.24 to 12.15 mg/L).

10.2.6.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

The two available, OECD TG compliant studies report LC_{50} values > 1 mg/L and < 5 mg/L. Clinical signs were similar to those recorded following oral administration. Necropsy of decedents and some survivors showed lung abnormalities.

10.2.6.3.2 Comparison with the GB CLP criteria

The lowest reliable LC_{50} value (i.e., 1.97 mg/L (male only) reported in Merkel (2001)) lies within the range ($1 < LC_{50} \leq 5$ mg/L), which supports classification as Acute Inhalation Tox. 4 (H332: Harmful if inhaled).

10.2.6.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Based on the results of the acute inhalation toxicity studies, Bordeaux mixture meets the classification criteria for Acute Tox. 4 (H332: Harmful if inhaled). This is consistent with the existing entry for this substance on the GB MCL list. The Agency proposes an ATE of 1.97 mg/L (dusts or mists).

10.2.7 Copper flakes (coated with aliphatic acid)

Copper flakes (coated with aliphatic acid) may also be referred to as coated copper flake.

10.2.7.1 Oral route

Table 44: Summary of animal studies on acute oral toxicity for copper flakes (coated with aliphatic acid), based on information in CLH (2013g)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 403, with deviations GLP	Rat, Sprague-Dawley	Coated copper flake Purity: not stated Vehicle: arachis oil BP	3 females at 2000 mg/kg bw and 3 female and 3 male at 200 mg/kg bw Acute exposure 14 days post exposure	LD_{50} = 300-500 mg/kg bw combined	Sanders A. (2001d)

Sanders A. (2001d)

OECD 423

GLP

Deviations: Yes

1) Information of the test material including the batch no and the purity were not provided;

2) No justification for the choice of vehicle was provided;

3) Due to a technical error, the presence of any macroscopic abnormalities for the female animal treated with 2000 mg/kg bw that was killed in extremis was not recorded.

These deviations are not considered to have influenced the integrity of the study.

Method

A group of 3 fasted female Sprague-Dawley rats were treated with 2000 mg/kg bw. Based on the results from this dose level further groups of 3 male and 3 female fasted animals were treated at a dose level of 200 mg/kg bw. Dosing was performed sequentially. The test material was administered orally via gavage as a suspension in arachis oil BP.

The animals were observed for deaths or overt signs of toxicity ½, 1, 2, and 4 hours after dosing and subsequently once daily up to 14 days.

At the end of the observation period the surviving animals were killed and subject to a gross necropsy.

Results

Two animals treated with 2000 mg/kg bw were found dead 5 days after dosing. One animal treated with 2000 mg/kg bw was killed in extremis eight days after dosing. There were no deaths noted at 200 mg/kg bw. Signs of systemic toxicity noted in animals treated with 2000 mg/kg bw were hunched posture, lethargy, pilo-erection, diarrhoea, decreased respiratory rate, laboured respiration, ataxia, pallor of the extremities, emaciation, tiptoe gait and faeces stained green. Hunched posture was noted during the day of dosing and one day after dosing in one male treated with 200 mg/kg bw. No other signs of systemic toxicity were noted in animals treated with 200 mg/kg bw. The surviving animals showed expected gains in bodyweight over the study period.

At necropsy, animals treated with 2000 mg/kg bw that died during the study had abnormalities including red lungs, dark liver, dark kidneys, copper-coloured material

present in the stomach, haemorrhagic gastric mucosa, sloughing of the no-glandular epithelium of the stomach and haemorrhagic small and large intestines. No abnormalities were noted at necropsy of animals treated with 200 mg/kg bw.

The LD_{50} of the test material was estimated to be in the range of 300-500 mg/kg bw.

10.2.7.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

One guideline study is available in rats. The acute oral LD_{50} was estimated to be in the range of 300-500 mg/kg bw for males and females.

10.2.7.1.2 Comparison with the GB CLP criteria

In a guideline study, the oral LD_{50} values for males and females were in the range 300-500 mg/kg bw, which supports classification as Acute Tox.4 (H302: Harmful if swallowed).

10.2.7.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results of the acute oral toxicity studies, copper flake (coated with aliphatic acid) meet the criteria for classification as Acute Tox.4 (H302: Harmful if swallowed) which is consistent with the existing GB MCL list entry. The Agency proposes an ATE of 500 mg/kg bw, based on Table 3.1.2 of Annex I of CLP.

10.2.7.2 Dermal route

Not relevant for this MCL report.

10.2.7.3 Inhalation route

Table 45: Summary of animal studies on acute inhalation toxicity for copper flakes (coated with aliphatic acid), based on information in CLH (2013g)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form, and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
OECD 403	Rat Sprague-	Coated copper flake	0.59-2.13 mg/L	LC_{50} (4 h) = 1.03 mg/l (Males and	Wessen CM. (2001)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form, and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
GLP	Dawley 5 or 10/sex/group	Purity: not stated Dust (MMAD =4.49-5.86µm)	Nose only 4-hour exposure 14 days post exposure	females combined) LC_{50} (4 h) = 0.733 mg/l (Males only) LC_{50} (4 h) = 1.67 mg/l (Females only)	

Wessen CM. (2001)

OECD 403

GLP

Deviations: None

Method

The study was designed to investigate the acute inhalation toxicity potential of coated copper flake following a single (nose only) exposure of 4 hours.

Groups of 5 or 10 Sprague-Dawley rats (5 males and/or 5 females) were exposed to a dust atmosphere of copper at mean achieved atmospheric concentrations of 2.13, 1.68, 1.12, 0.84 or 0.59 mg/l as summarised in table 46 below.

Table 46: Mean achieved atmospheric concentrations (mg/l) in Wessen (2001) (Reproduced from CLH, 2013g).

Group	Nominal	Mean Achieved Atmospheric Concentration (mg/l)	No of Males	No of females
5	10.2	2.13	0	5
3	6.41	1.68	0	5
1	2.64	1.12	5	5
4	2.52	0.84	5	0
2	1.65	0.59	5	0

The percentage of inhalable particles (reported as < 4 µm) was in the range of 36.3-45.4%; the Mean Mass Median Aerodynamic Diameter of particles was in the range of 4.49-5.86 µm.

Table 47:**The percentage of inhalable particles and Mean Mass Median Aerodynamic Diameter in Wessen CM. (2001). (Reproduced from CLH, 2013).**

Group	Nominal	Mean Mass Median Aerodynamic Diameter (µm)	Inhalable Fraction (% < 4 µm)	Geometric Standard Deviation
5	10.2	5.86	36.3	2.94
3	6.41	5.34	38.8	2.73
1	2.64	4.49	45.4	2.74
4	2.52	5.57	38.6	3.12
2	1.65	5.26	40.8	3.25

All animals were observed for clinical signs at hourly intervals during exposure, immediately on removal from the restraining tubes at the end of exposure, 1 hour after termination of exposure and subsequently once daily for up to 14 days. Any mortalities or evidence of overt toxicity were recorded at each observation. Individual body weights were recorded prior to treatment on the day of exposure and on days 7 and 14 or at death.

All animals, including those that died during the study, were subjected to a full external; and internal examination, any macroscopic abnormalities were recorded. The respiratory tract was subjected to a detailed macroscopic examination for signs of irritancy or local toxicity.

Results

At 2.13, 1.68, 1.12, 0.84 and 0.59 mg/l, 4/5, 2/5, 5/10, 4/5 and 1/5 animals died respectively. All deaths occurred within 24h of exposure to the test substance. Male animals appeared less tolerant to the material with the earliest death recorded after 3 hours exposure at a mean of 1.12 mg/L (highest concentration used for the male exposures). This compares with the earliest female death recorded immediately after the completion of the 4-hour exposure at a mean concentration of 1.68 mg/L.

Dose Group 5- 2.13 mg/l

During exposure, decreased respiratory rate, laboured respiration and wet fur were noted in all animals and there were instances of increased respiratory rate and fur staining by the test material. Upon removal from the chamber, animals showed decreased or increased respiratory rate, laboured respiration, hunched posture, piloerection, fur staining by the test

material and wet fur and well as instances of pallor of the extremis, ataxia, noisy respiration and cyanosis. One hour after removal, a slight worsening in the condition of the surviving animals was observed. Post exposure, the surviving animal recovered relatively quickly to appear normal from day 4.

Dose Group 3- 1.68 mg/l.

During exposure, decreased respiratory rate, fur staining by the test material and wet fur were noted in all animals and laboured respiration was common. Upon removal from the chamber, surviving animals showed decreased or increase respiratory rate, noisy respiration, ataxia, hunched posture, piloerection, fur staining by the test material and wet fur. There were also instances of laboured respiration, pallor of the extremities, and ptosis. One hour after removal, a deterioration in the condition of the animals was observed, with hypothermia now observed for all animals.

Post exposure, animals made a steady recovery. However, clinical signs including hunched posture and noisy respiration persisted. From day 6, 2 animals appeared asymptomatic but noisy respiration persisted throughout the observation period for the other survivor.

Dose Group 1- 1.12mg/l

During exposure, decreased or increased respiratory rate and wet fur were noted in all animals and laboured respiration and fur staining by the test material were common. On removal from the chamber, surviving animals showed decreased respiratory rate, noisy respiration, hunched posture, piloerection, fur staining by the test material and wet fur whilst ataxia, pallor of the extremities, cyanosis, lethargy, and ptosis were frequently seen. On hour after removal little change in the surviving males was observed, whilst the condition of the female animals had deteriorated slightly.

Post exposure, animals made a steady recovery. However clinical signs such as hunched posture and noisy respiration persisted. Female animals appeared asymptomatic from day 8 but noisy respiration persisted until day 12 for the surviving male.

Dose Group 4 – 0.84mg/l

During exposure, decreased or increased respiratory rate wand wet fur were noted in all animals and laboured respiration and fur staining by the test material were common. On removal from the chamber, surviving males showed increased respiratory rate, laboured and noisy respiration, pallor of the extremities, ptosis, hunched posture, piloerection, fur staining by the test material and wet fur and ataxia was recorded for most of the animals. Little change in the condition of the animals was observed 1 hour following removal.

Post exposure, the remaining surviving animal recovered quickly and appeared normal from day 3.

Dose Group 2- 0.59mg/l

Decreased or increased respiratory rate and wet fur were noted in all animals and there was a single instance of laboured respiration during exposure. Upon removal from the chamber, animals showed decreased or increased respiratory rate, noisy respiration, hunched posture, piloerection, fur staining by the test material and wet fur. There were also instances of laboured respiration, ataxia and cyanosis. Slight signs of recovery were observed in 3 animals 1 hour after removal, whilst the condition of the remaining 2 had deteriorated slightly.

Post exposure, respiratory observations diminished over several days. The only remaining clinical sign in surviving animals was hunched posture. From day 6, 1 animal appeared normal, and all animals were asymptomatic from day 8.

Generally, signs of wet fur, hunched posture, piloerection and red/brown staining around the snout and/or eyes are commonly seen in animals for short periods on removal from the chamber following 4-hour inhalation studies. These observations are considered to be associated with the restraint procedure and, in isolation, are not indicative of toxicity.

Table 48: Wessen (2001) - summary of findings (reproduced from CLH, 2013g)

Dose (mg/l)	Number of dead/number of investigated	Time of death (range)	Observations
2.13	4/5	Day 1	Common clinical observations noted during the study included decreased respiratory rate, laboured respiration, noisy respiration, hunched posture and piloerection. There were instances of increased respiratory rate, cyanosis, ataxia, pallor of the extremities and ptosis whilst tiptoe gait, lethargy, sneezing and hypothermia were noted sporadically. Reduced bodyweight gain or weight loss was noted in most surviving animals during the first week of the recovery period. All surviving animals showed an overall body weight gain at the end of the treatment period. Gross necropsy of premature decedents and surviving animals showed abnormal findings in the lungs (enlarged, dark patches, pale, pale patches, dark foci, fluid filled, discolouration, haemorrhagic, abnormally dark) and less frequently in the liver (patchy pallor), small intestine (gaseous distension, dark contents) and large intestine (gaseous distension).
1.68	2/5	Day 1	
1.12	5/10	Day 1	
0.84	4/5	Day 1	
0.59	1/5	Day 1	
LC_{50} (4h)=1.03 mg/l			

Reduced bodyweight gain or weight loss was noted in most surviving animals during the first week of the recovery period, all surviving animals showed an overall bodyweight gain at the end of the treatment period.

There were no abnormal gross necropsy findings in 3 rats (1 surviving male and 1 surviving female from group 1, and 1 surviving male from group 4).

Gross necropsy of the remaining premature decedents and surviving animals showed abnormal findings in the lungs (enlarged, dark patches, pale, pale patches, dark foci, fluid filled, discolouration, haemorrhagic, abnormally dark) and less frequently in the liver (patchy pallor), small intestine (gaseous distension, dark contents) and large intestine (gaseous distension).

The LC_{50}s as reported by this study are as follows:

Males and females combined: LC_{50} (4 h) = 1.03 (0.692 - 1.55) mg/l

Males only: LC_{50} (4 h) = 0.733 (0.609 - 0.838) mg/l

Females only: LC_{50} (4 h) = 1.67 (1.41 1.99) mg/l

10.2.7.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

The acute inhalation LC_{50} in the rat were:

LC_{50} (4 h) = 1.03 mg/l (males and females combined)

LC_{50} (4 h) = 0.733 mg/l (males only)

LC_{50} (4 h) = 1.67 mg/l (females only)

10.2.7.3.2 Comparison with the GB CLP criteria

The lowest LC_{50} of 0.733 mg/l (for males) lies within the range (0.5-1 mg/l) for classification as Acute Tox.3 (H331: Toxic if inhaled).

10.2.7.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Copper flakes coated with aliphatic acid meet the classification criteria for Acute Tox. 3 (H331: Toxic if inhaled) which is consistent with the existing entry on the GB MCL list. The Agency proposes an ATE of 0.733 mg/L (dusts or mists).

10.2.8 tetracopper hexahydroxide sulphate; [1] tetracopper hexahydroxide sulphate hydrate [2]

Tetracopper hexahydroxide sulphate; [1] tetracopper hexahydroxide sulphate hydrate [2] may also be referred to as tribasic copper sulphate.

10.2.8.1 Oral route

Table 49: Summary of animal studies on tetracopper hexahydroxide sulphate; [1] tetracopper hexahydroxide sulphate hydrate [2], based on information in CLH (2013h)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 423 GLP	Rat Sprague Dawley 3/sex/dose	Tribasic copper sulphate Purity: 98.4% (w/w tribasic copper sulphate); 54.2% (w/w copper) Vehicle: 0.5% carboxymethyl cellulose	200-2000 mg/kg bw. Acute exposure 14 days post exposure	Estimated to be between 300 and 500 mg/kg bw.	Sanders, A. (2002a)

Sanders, A. (2002a)

OECD 423

GLP

Deviations: None

Method

Sprague-Dawley CD rats (groups of 3 males and 3 females) were administered tribasic copper sulphate (batch number L2206, containing 54.2% w/w copper, content of tribasic copper sulphate 98.4%) as a dispersion in 0.5% carboxymethyl cellulose. Dose levels of 200 mg/kg bw (males and females) and 2000 mg/kg bw (females only) were administered by single oral administration (gavage). Animals were observed frequently on the day of dosing and the once daily for the 14-day post-dosing period. Animals were weighed prior to administration and after 7 days (on day 8) and after 14 days (on day 15) or at death. Decedents and animals surviving to 14 days were subject to gross necropsy.

Results

There were no mortalities at 200 mg/kg bw. At 2000mg/kg bw, all females died, with the deaths occurring on day 1 or day 2. There was a variety of clinical signs recorded in females including piloerection, hunched posture and diarrhoea at both 200 and 2000 mg/kg bw, and lethargy, decreased respiration rate, laboured respiration and ataxia at 2000 mg/kg bw only. Symptoms occurred on day 1 and all females dosed at 200 mg/kg had recovered by day 2. No symptoms occurred in males dosed at 200 mg/kg. A summary of mortalities is presented in table 50 below.

Surviving animals showed weight gain during the study. No gross necropsy findings were recorded in surviving animals. Necropsy findings in animals which died during the study were a blue coloured liquid in the stomach, haemorrhagic or abnormally red lungs, dark liver, dark kidneys, epithelial sloughing of the gastric mucosa and non-glandular region of the stomach and haemorrhagic or abnormally red lungs, dark liver, dark kidneys, epithelial sloughing of the gastric mucosa and non-glandular region of the stomach and haemorrhagic small intestine.

Table 50: Mortalities reported in Sanders (2002a) following oral administration of tribasic copper sulphate to rats. (Reproduced from CLH, 2013h)

Dose (mg/kg bw)	Males		Females	
	Mortality	Time of death	Mortality	Time of death
200	0/3	-	0/3	-
2000	-	-	3/3	Day 1 (2); Day 2

Figures in parenthesis are the number which died on the day specified if more than one.

The acute oral LD_{50} of tribasic copper sulphate to the rat was estimated to be between 300 and 500 mg/kg bw for females.

10.2.8.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Tribasic copper sulphate was of moderate toxicity via the oral route with an estimated LD_{50} of between 300 and 500 mg/kg bw.

Following exposure there were a range of clinical signs including diarrhoea, piloerection, ataxia, lethargy, hunched posture and impaired respiration. At necropsy, surviving animals generally showed no gross findings at however, animals which died during the studies showed discoloration or haemorrhage in the digestive tract, effects on liver and/or kidney

and substances similar to the test material were found to be present in the stomach or intestines.

10.2.8.1.2 Comparison with the GB CLP criteria

For tetracopper hexahydroxide sulphate; [1] tetracopper hexahydroxide sulphate hydrate [2], the oral LD_{50} in rats can be identified as between 300 and 500 mg/kg. The oral LD_{50} lies within the range (300-2000 mg/kg) for classification as Acute Tox.4 (H302: Harmful if swallowed). As the available study did not identify a specific LD_{50}, the default ATE of 500 mg/kg bw is appropriate (Table 3.1.2 of Annex I of CLP).

10.2.8.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results of the acute oral toxicity studies, tetracopper hexahydroxide sulphate; [1] tetracopper hexahydroxide sulphate hydrate [2] meets the criteria for classification as Acute Oral Tox. 4 (H302: Harmful if swallowed), which is consistent with the existing GB MCL list entry. As a specific ATE could not be identified, the Agency proposes an ATE of 500 mg/kg bw (converted acute toxicity point estimate; see Table 3.1.2, Annex 1 of GB CLP).

10.2.8.2 Dermal route

Not relevant for this MCL report.

10.2.8.3 Inhalation route

Not relevant for this MCL report.

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

Not relevant for this MCL report.

10.4 Skin corrosion/irritation

Not relevant for this MCL report.

10.5 Serious eye damage/eye irritation

Not relevant for this MCL report.

10.6 Respiratory sensitisation

Not relevant for this MCL report.

10.7 Skin sensitisation

Not relevant for this MCL report.

10.8 Specific target organ toxicity – repeated exposure (STOT RE)

Not relevant for this MCL report.

10.9 Germ cell mutagenicity

Not relevant for this MCL report.

10.10 Carcinogenicity

Not relevant for this MCL report.

10.11 Reproductive toxicity

Not relevant for this MCL report.

10.12 Aspiration hazard

Not relevant for this MCL report.

11 Evaluation of environmental hazards

Not relevant for this MCL report.

11 Evaluation of additional hazards

10.12 Hazardous to the ozone layer

Not relevant for this MCL report.

11 Additional labelling

Not relevant for this MCL report.

11 References

Copper (I) oxide

CLH (2013a) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Dicopper Oxide; Date: 2013; Written by: ANSES (on behalf of the French MSCA) Accessed date: 02/2024; Available at: CLH report for Dicopper oxide; Copper (I) oxide

ECHA (2014a) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Dicopper oxide; Reference CLH-O-0000001412-86-31/F; Date: 04/12/2014, Accessed date: 02/2024; Available at: RAC opinion for Dicopper oxide; Copper (I) oxide

Copper (II) hydroxide

CLH (2013b) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Copper (II) hydroxide; Date: 2013; Written by: ANSES (on behalf of the French MSCA) Accessed date: 02/2024; Available at: CLH report for Copper (II) hydroxide, copper dihydroxide

ECHA (2014b) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Copper (II) hydoxide; Reference CLH-O-0000001412-86-44/F; Date: 04/12/2014, Accessed date: 02/2024; Available at: RAC opinion for Copper (II) hydroxide, copper dihydroxide

Copper (II) carbonate – Copper (II) hydroxide (1:1)

CLH (2013c) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Copper (II) carbonate; Date: 2013; Written by: ANSES (on behalf of the French MSCA) Accessed date: 02/2024; Available at: CLH report for Copper (II) carbonate - copper (II) hydroxide (1:1)

ECHA (2014c) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Copper (II) carbonate; Reference CLH-O-0000001412-86-41/F; Date: 04/12/2014, Accessed date: 02/2024; Available at: RAC opinion for Copper (II) carbonate – copper (II) hydroxide (1:1)

Dicopper chloride trihydroxide

CLH (2013d) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Dicopper chloride trihydroxide; Date: 2013; Written by: ANSES (on behalf of the French MSCA) Accessed date: 02/2024; Available at: CLH report for Dicopper chloride trihydroxide

ECHA (2014d) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Dicopper chloride trihydroxide; Reference CLH-O-000001412-86-43/F; Date: 04/12/2014, Accessed date: 02/2024; Available at: RAC opinion for Dicopper chloride trihydroxide

Copper sulphate pentahydrate

CLH (2013e) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Copper sulphate pentahydrate; Date: 2013; Written by: ANSES (on behalf of the French MSCA) Accessed date: 02/2024; Available at: CLH report for Copper sulphate pentahydrate

ECHA (2014e) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Copper sulphate pentahydrate; Reference CLH-O-0000001412-86-33/F; Date: 04/12/2014, Accessed date: 02/2024; Available at: RAC opinion for Copper sulphate pentahydrate

Bordeaux mixture

CLH (2013f) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Bordeaux mixture; Date: 2013; Written by: ANSES (on behalf of the French MSCA) Accessed date: 02/2024; Available at: CLH report for Bordeaux mixture, reaction products of copper sulphate with calcium dihydroxide

ECHA (2014f) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Bordeaux mixture; Reference CLH-O-0000001412-86-36/F; Date: 04/12/2014, Accessed date: 02/2024; Available at: RAC opinion for Bordeaux mixture, reaction products of copper sulphate with calcium dihydroxide

Copper flakes (coated with aliphatic acid)

CLH (2013g) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Copper flakes (coated with aliphatic acid); Date: 2013; Written by:

ANSES (on behalf of the French MSCA) Accessed date: 02/2024; Available at: CLH report for Copper flakes (coated with aliphatic acid)

ECHA (2014g) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Copper flakes (coated with aliphatic acid); Reference CLH-O-0000001412-86-30/F; Date: 04/12/2014, Accessed date: 02/2024; Available at: RAC opinion for Copper flakes (coated with aliphatic acid)

Tetracopper hexahydroxide sulphate [1], Tetracopper hexahydroxide sulphate hydrate [2]

CLH (2013h) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Tetracopper hexahydroxide sulphate [1], Tetracopper hexahydroxide sulphate hydrate [2]; Date: 2013; Written by: ANSES (on behalf of the French MSCA) Accessed date: 02/2024; Available at: CLH report for tetracopper hexahydroxide sulphate; [1] tetracopper hexahydroxide sulphate hydrate [2]

ECHA (2014h) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Tetracopper hexahydroxide sulphate [1], Tetracopper hexahydroxide sulphate hydrate [2]; Reference CLH-O-0000001412-86-42/F; Date: 04/12/2014, Accessed date: 02/2024; Available at: RAC opinion for tetracopper hexahydroxide sulphate; [1] tetracopper hexahydroxide sulphate hydrate [2]

11 Annexes

Not applicable.

Further information

This publication is available on the HSE website.

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