Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Copper(II) oxide

EC number: 215-269-1
CAS number: 1317-38-0

CLH-O-0000001412-86-45/F

Adopted

04 December 2014

4 December 2014

CLH-O-0000001412-86-44/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemicals name: Copper (II) oxide

EC number: 215-269-1

CAS number: 1317-38-0

The proposal was submitted by **France** and received by the RAC on **19 July 2013.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories.

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **18 December 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **3 February 2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Stephen Dungey**

Co- rapporteur, appointed by RAC: **Marja Pronk**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation. The comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was reached on **4 December 2014**.

The RAC opinion was adopted by **consensus**.

OPINION OF THE RAC

RAC adopted the opinion that **Copper(II) oxide** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	n/a										
dossier submitters proposal	029-016-00-6	copper(II) oxide	215-269-1	1317-38-0	Acute Tox. 2 Aquatic Acute 1 Aquatic Chronic 1	H330 H400 H410	GHS06 GHS09 Dgr	H330 H410		M=10 M=1	
RAC opinion	029-016-00-6	copper(II) oxide	215-269-1	1317-38-0	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09	H410		M=100 M=100	
Resulting Annex VI entry if agreed by COM	029-016-00-6	copper(II) oxide	215-269-1	1317-38-0	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09	H410		M=100 M=100	

SCIENTIFIC GROUNDS FOR THE OPINION

RAC general comment

In addition to copper(II) oxide, ECHA received CLH proposals for nine other copper compounds or forms of copper from the same dossier submitter (France). The dossier submitter stated that during systemic toxicity, the toxicologically relevant moiety is the Cu^{2+} ion, which is released to a different degree from all the copper compounds. A comparison of the bioavailability (and hence toxicity) of various copper compounds showed that bioavailability is highest for the most soluble compound copper sulphate. Consequently, the use of copper sulphate data would represent a worst-case scenario for the determination of the systemic toxicity of relatively insoluble copper compounds. For the systemic endpoints the dossier submitter therefore proposed to read-across between the different copper compounds, and introduced identical sections on specific target organ toxicity, mutagenicity, carcinogenicity and reproductive toxicity in the CLH reports for all compounds. The studies reported in these common sections mostly concern copper sulphate pentahydrate, sometimes also other copper compounds. The sections on acute toxicity, skin irritation/corrosion, eye damage/irritation and sensitisation in the CLH reports are specific for each substance/form.

RAC considered the dossier submitter's proposal to group the substances together for consideration of STOT RE and the CMR endpoints. RAC noted that differences in solubility and other physico-chemical properties may potentially impact the toxicity of the various copper compounds, in particular locally after inhalation exposure. RAC noted further that the anions, in particular thiocyanate, might also be a contributing factor to the toxicity. However, these aspects were not addressed in the CLH reports, whereas RAC concluded that these would need a more detailed analysis. As none of the studies with Copper(II) oxide or the other tested copper compounds yielded positive evidence for the classification of these endpoints, RAC did not pursue the aspect of grouping the nine substances any further.

RAC evaluation of physical hazards

Summary of the Dossier submitter's proposal

Copper(II) oxide is a stable inorganic compound with copper in a high oxidation state. Its physicochemical properties indicate that it is neither explosive, flammable nor self-reactive. A study showed that it does not have oxidising properties (Desai, 1992). The dossier submitter proposed no classification for physical hazards.

Comments received during public consultation

No comments were received during the public consultation.

Assessment and comparison with the classification criteria

Since copper(II) oxide does not have explosive or oxidising properties and is not (auto-)flammable, RAC supports the non-classification for physical hazards, as proposed by the dossier submitter.

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Two acute toxicity studies are included in the CLH report, both conducted with copper(II) oxide in rats. An oral limit dose study (in accordance with OECD TG 423) with six male rats reported no mortalities at 2000 mg/kg bw (Sanders, 2002d). A dermal limit dose study (in accordance with OECD TG 402) reported no mortalities when five male and five female rats were administered 2000 mg/kg bw (Sanders, 2002b). No classification was proposed for acute oral and dermal toxicity.

According to the dossier submitter, no data are available on acute inhalation toxicity of copper(II) oxide. However, as several salts of copper are classified for acute inhalation toxicity, the dossier submitter proposed to read across from copper dihydroxide (= copper(II) hydroxide) as both copper(II) oxide and copper dihydroxide have copper in the same oxidative state (Cu^{2+}), have roughly similar molecular mass, and have very similar solubility at different pHs. The dossier submitter therefore proposed Acute Tox. 2 – H330 for copper(II) oxide, similar to their proposal for copper dihydroxide. Following comments received during public consultation this proposal was however withdrawn by the dossier submitter (see section *Comments received during public consultation* below).

The CLH report also contains a review of seven studies reporting on a possible association between copper exposure and Metal Fume Fever (MFF) in humans (Borak *et al.*, 2000). MFF presents as an influenza-like illness with cough and dyspnoea followed by fever, sweating and shivering, accompanied by nausea, headache, weakness, a sweet metallic taste and muscle and joint pain. The dossier submitter concluded (in agreement with the authors of the review) that none of the reports contain enough conclusive evidence to associate copper fumes or particles with MFF. Another review (Chuttani *et al.*, 1965) reports on several cases of self-poisoning by oral ingestion of copper sulphate. Intoxication is associated with nausea, epigastric burning, vomiting, diarrhoea, ulcerations of the gastric and intestinal mucosa, and liver and kidney histopathology. Rapid chelation therapy increases survival.

Comments received during public consultation

Two MSCAs and two industry organisations disagreed with the proposed classification for acute inhalation toxicity. One MSCA requested more justification as no acute inhalation toxicity study is available for copper(II) oxide, while another MSCA questioned the validity of the read-across from copper dihydroxide. This because the acute oral toxicity of copper dihydroxide is clearly higher than that of copper(II) oxide, which would suggest that applying Acute Tox. 2 – H330 to copper(II) oxide is over conservative. In addition to the above objections, the two industry organisations argued that copper(II) oxide has a low bioavailability relative to other copper compounds (due to lower solubility in water and artificial lung fluid) and that due to its large particle size (MMAD >60 µm) more than 95% of the material deposited in the respiratory tract will be translocated to the gastrointestinal tract. The latter implies that the acute toxicity will be determined by that of the oral route, which was shown to be very low. This makes it unlikely that copper(II) hydroxide is acutely toxic via inhalation. They further point out that in the voluntary risk assessment report on copper and its compounds (from 2007, available on the ECHA website) a justification was provided for derogating testing for acute inhalation toxicity for copper(II) oxide, and a conclusion was drawn that copper(II) oxide does not require classification for this endpoint. In response, the dossier submitter agreed with the arguments presented by the commenting parties and noted that in addition there is also no evidence that copper(II) oxide is implicated in MFF. The dossier submitter therefore changed the original proposal (Acute Tox. 2 – H330) into a no classification proposal for acute inhalation toxicity.

Assessment and comparison with the classification criteria

Following a comparison of the LD_{50} values in the key studies with the criteria, RAC agrees with the conclusion of the dossier submitter that copper(II) oxide should not be classified for acute oral and dermal toxicity.

For the inhalation route, RAC supports the arguments put forward during public consultation that read-across from copper dihydroxide is not appropriate. Although no acute inhalation toxicity study is available for copper(II) oxide, RAC, in line with commenting parties, is of the opinion that the solubility and particle size characteristics and the very low acute toxicity via other routes make it unlikely that copper(II) oxide is acutely toxic via inhalation. Available human data also do not warrant classification. Hence, RAC agrees with the revised conclusion that classification of copper(II) oxide for acute inhalation toxicity is not warranted.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal
In the absence of any specific toxic effects on organs reported in the acute toxicity studies, the dossier submitter concluded that no classification is warranted for STOT SE.

Comments received during public consultation
No comments were received during the public consultation.

Assessment and comparison with the classification criteria
In the available acute toxicity studies with rats, no clinical signs of toxicity or signs of skin irritation were observed. In human self-poisoning cases the most frequently observed symptoms (nausea, epigastric burning, vomiting, diarrhoea) are indicative of non-specific, general acute toxicity. RAC therefore supports the conclusion of the dossier submitter that copper(II) oxide should not be classified for specific target organ toxicity – single exposure (STOT SE).

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal
One rabbit skin irritation study, conducted with copper(II) oxide according to OECD TG 404, is reported in the CLH report (Sanders, 2002a). Copper(II) oxide did not cause oedema or erythema in any animal (n=3) at any time point. The dossier submitter concluded that no classification for skin irritation is warranted.

Comments received during public consultation
No comments were received during the public consultation.

Assessment and comparison with the classification criteria
Given that all three test-animals scored zero for both erythema and oedema over 24/48/72h in the available skin irritation study, RAC agrees with the conclusion of the dossier submitter that copper(II) oxide should not be classified for skin irritation.

RAC evaluation of eye damage/irritation

Summary of the Dossier submitter's proposal
One rabbit eye irritation study, conducted with copper(II) oxide according to OECD TG 405, is reported in the CLH report (Sanders, 2002c). No individual scores were reported for the three animals tested, only mean scores over all animals. Mean scores over 24-72h were 0.33 for corneal opacity, 0.22 for iritis, and 0.77, 0.55 and 0.66 for conjunctival redness, chemosis and discharge, respectively. All treated eyes eyes appeared normal within or at 7 days after treatment. As the mean scores were below 1 for corneal opacity and iritis and below 2 for conjunctival effects, the dossier submitter proposed no classification for eye irritation.

Comments received during public consultation
No comments were received during the public consultation.

Assessment and comparison with the classification criteria
In the available eye irritation study, slight corneal opacity (up to 72h) and iritis (up to 48h) were each observed in one test animal. Moderate conjunctival irritation was observed in all treated animals from 1 h after treatment. All effects were reversible within 7 days. With mean scores over 24-72h below the threshold values for classification (≥1, ≥1, ≥2 and ≥2 for corneal opacity, iritis, conjunctival redness and chemosis, respectively, in at least 2 of 3 tested animals), RAC agrees with the conclusion of the dossier submitter that copper(II) oxide should not be classified for eye irritation.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

One guinea pig maximisation test (GPMT), performed with copper(II) oxide according to OECD TG 406, was included in the CLH report (Sanders, 2002e). For induction, an intradermal injection of 0.1% (w/w) at day 1 and topical application of 75% (w/w) at day 7 were used. Animals were challenged with 10% (w/w) and 5% (w/w) topical application on day 21. The findings at 24h and 48h after challenge are presented in the table below.

	24 hrs			**48 hrs**		
	control	5%	10%	control	5%	10%
Black/grey coloured staining*	3/5 1/5	 1/10	8/10	3/5 1/5	 1/10	7/10
Erythema	0/5	2/10	4/10	0/5	0/10	0/10
Oedema	0/5	0/10	0/10	0/5	0/10	0/10

* was reported not to affect evaluation of skin responses

As the erythema disappeared after 48h, the dossier submitter considered it not to be associated with contact sensitisation.

A few clinical cases of allergic dermatitis upon copper exposure and skin reactions following use of copper-based intrauterine contraceptive devices have been reported, but overall the findings indicate that in comparison with other metals, copper was relatively rarely a cause of allergic contact dermatitis. The dossier submitter concluded, based on what they consider negative GPMT and the rare cases of allergic reactions to copper compounds in humans, that no classification for skin sensitisation for copper(II) oxide is warranted.

Comments received during public consultation

No comments were received during the public consultation.

Assessment and comparison with the classification criteria

A substance is considered to be a skin sensitiser if, in a GPMT, a positive response is observed in at least 30% of the treated animals at an intradermal induction concentration of ≤0.1%. The result at 24h following the 10% (w/w) challenge concentration, with 4/10 (40%; net incidence) animals positive for erythema (no scores given), fulfils this criterion. The erythema in these animals had reversed by 48h (net incidence 0%). The rapid reversion could point to primary irritation rather than sensitisation, but it is noted that no erythema (or oedema) was observed in the acute dermal toxicity test and in the skin irritation test with copper(II) oxide. There are no indications in the CLP criteria/guidance on a possible effect of reversibility on the classification, so in principle the GPMT is considered positive, albeit weakly. When considering the human evidence for skin sensitisation due to copper compounds, the few individual cases of allergic reactions reported indicate that this is a relatively rare finding, and thus insufficient to warrant classification. After weighing all available information, RAC supports the conclusion of the dossier submitter that classification of copper(II) oxide as skin sensitiser is not warranted.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

No data on copper(II) oxide are available in the CLH report. However, in light of the proposal to read-across between the different copper compounds for systemic endpoints (see section "RAC general comment" above), the dossier submitter included in the CLH report several animal studies with repeated exposure to other copper compounds (predominantly copper sulphate pentahydrate) for various durations and routes, as well as some human data.

Hébert *et al.* (1993) reported on oral 15-day drinking water and feeding studies and 90-day feeding studies in both rats and mice, all conducted with copper sulphate pentahydrate but none guideline compliant. In addition, three studies where copper sulphate was administered in the diet

at one or several doses for up to 15 weeks and animals sacrificed at several intervals, were also reported (Haywood, 1980, 1985; Haywood & Comerford, 1980). One OECD TG 412 compliant 28-day rat inhalation study conducted with dicopper oxide (Kirkpatrick, 2010) is included as well as an older non-guideline compliant study where guinea pigs were exposed via inhalation to Bordeaux mixture for about 6 months (Pimentel & Marques, 1969). Finally, an OECD TG 410 compliant dermal rabbit study is included (Paynter, 1965), with exposure to copper dihydroxide for 3 weeks (5 days per week). A human case study of chronic oral self-administration of copper causing liver failure (O'Donohue *et al.*, 1993) and human volunteer studies demonstrating nausea associated with copper sulphate in drinking water (Araya *et al.*, 2001, 2003) are also reported, as are human case studies of chronic inhalation exposure to Bordeaux Mixture causing pulmonary lesions (e.g. Pimentel & Marques, 1969; Pimentel & Menezes, 1975, 1977).
Inhalation exposure to dicopper oxide resulted in no irreversible adverse effects up to the highest dose tested in rats (2 mg/m^3). Following dermal exposure to rabbits, degenerative skin abnormalities were only observed at 1000 but not at 500 mg copper/kg bw/day. Human data is poorly reported and doses are difficult to estimate. Following oral exposure in rats, target organs of copper were the liver (inflammation), kidneys (histopathological changes) and forestomach (hyperplasia and hyperkeratosis), with some evidence of haematological changes. Mice were less sensitive, with adverse effects limited to the forestomach. According to the dossier submitter, no serious adverse effects were observed in the available oral studies below the cut-off value for classification (100 mg/kg bw/day for a 90-day study). After considering all available human and animal data, the dossier submitter concluded that they do not support classification for specific target organ toxicity following repeated exposure.

Comments received during public consultation
No comments were received during the public consultation.

Assessment and comparison with the classification criteria
RAC notes that no data are available on copper(II) oxide. The CLH report contains data on other copper compounds (predominantly copper sulphate pentahydrate), from which the dossier submitter proposed to read-across to copper(II) oxide. In view of the considerations presented in the section "RAC general comment", RAC has not pursued the aspect of grouping any further. RAC concludes that in the absence of relevant data no proposal for classification for specific target organ toxicity following repeated exposure can be made for copper(II) oxide.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal
No data on copper(II) oxideare available in the CLH report. However, in light of the proposal to read-across between the different copper compounds for systemic endpoints (see section "RAC general comment" above), the dossier submitter included in the CLH report mutagenicity studies with other copper compounds (predominantly copper sulphate pentahydrate).

Ten *in vitro* studies were very briefly summarised in tabular form. Three Ames tests conducted with copper sulphate (pentahydrate) and another four conducted with Bordeaux Mixture, dicopper chloride trihydroxide, copper Nordox Technical and copper chloride were all reported as negative as well as a rec-assay with copper chloride. An unscheduled DNA synthesis (UDS) test conducted with copper sulphate in primary hepatocytes and an UDS and sister chromatid exchange (SCE) assay with copper nitrate in Chinese hamster V79 cells showed positive results in the absence of metabolic activation. The dossier submitter did not discuss these studies further in the report, as *in vitro* data are not considered appropriate to assess the genotoxic potential of copper. This is because absorbed copper is normally always bound to proteins in the body, where the *in vitro* tests present the cells with free copper, which is highly reactive.
Five *in vivo* studies are included in the CLH report, all conducted with copper sulphate pentahydrate. A negative mouse bone marrow micronucleus assay (Riley, 1994) and a negative rat liver USD assay (Ward, 1994) administering copper sulphate pentahydrate by gavage are presented. In addition, three studies administering copper sulphate pentahydrate by intra-peritoneal (IP) injection to mice are included. Two bone marrow chromosome aberration assays were concluded as positive as well as a sperm abnormality assay and one out of two

micronucleus assays (Bhunya & Pati, 1987; Agarwal et al., 1990; Tinwell & Ashby, 1990). Mice also scored positive for bone marrow chromosome aberrations following oral and subcutaneous administration of copper sulphate pentahydrate (Bhunya & Pati, 1987). Considering that the IP route bypasses the normal processing of copper in the body, that there were conflicting results for two IP micronucleus assays, and that two reliable studies via the oral route (where uptake is controlled by homeostatic mechanisms) were negative, the dossier submitter concluded that the available data do not support classification for germ cell mutagenicity for copper compounds, including copper(II) oxide.

Comments received during public consultation

For five of the ten copper compounds under consideration, one MSCA commented that the available genotoxicity data are insufficient to evaluate, and thus to conclude on, the genotoxic potential of copper compounds. The dossier submitter responded that in their opinion the data do not meet the criteria for classification, but acknowledged that insufficient evidence exists to exclude a genotoxic potential via the IP route, referring also to the EFSA peer review of copper substances (EFSA, 2008) where it was concluded that genotoxicity is not of concern upon oral administration, but that there is insufficient evidence to exclude a (local) genotoxic potential upon non-oral administration.

Assessment and comparison with the classification criteria

RAC notes that no data on copper(II) oxide are available. The CLH report contains data on other copper compounds (predominantly copper sulphate pentahydrate), from which the dossier submitter proposed to read-across to copper(II) oxide. In view of the considerations presented in the section "RAC general comment", and given that the available data on copper sulphate pentahydrate and some other copper compounds do not provide positive evidence for classification (see the RAC opinion on copper sulphate pentahydrate), RAC has not pursued the aspect of grouping any further. RAC concludes that in the absence of relevant data no proposal for classification for germ cell mutagenicity can be made for copper(II) oxide.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

No data on copper(II) oxide are available in the CLH report. However, in light of the proposal to read-across between the different copper compounds for systemic endpoints (see section "RAC general comment" above), the dossier submitter referred in the CLH report to several long-term animal studies with other copper compounds and to human data on copper exposure.

Several animal studies administering copper compounds in either drinking water or diet of rats and mice for various periods of time (up to two years) are presented. However, none meet the guidelines for carcinogenicity testing and several have shortcomings when it comes to evaluating carcinogenicity, such as short duration. None of the studies showed an indication of carcinogenic potential of copper administered systemically. Co-administration of copper with known carcinogens appeared to lower the risk of tumour formation in some cases.
Several cohort or epidemiological studies in humans exposed to copper through copper mining, smelting and refining are briefly summarised in the CLH report. The dossier submitter concluded that they provide little evidence for increased risk of cancer with exposure to copper compounds. Reference is also made to reports of the occupational disease Vineyard Sprayer's Lungs (VSL) associated with exposure to home-made Bordeaux Mixture. Due to poor reporting and possible confounders such as smoking, the dossier submitter concluded that a link between lung cancer and VSL cannot be established. There are two rare genetic diseases of copper in humans (Wilson's disease and Menkes' disease), but there is no evidence of increased incidences of cancer in patients with either disease, despite the chronic high tissue copper levels.
The dossier submitter concluded that the weight of evidence in humans and animals is that copper is not carcinogenic and that therefore no classification for carcinogenicity is warranted for copper compounds, including copper(II) oxide.

Comments received during public consultation
No comments were received during the public consultation.

Assessment and comparison with the classification criteria
RAC notes that no data are available on copper(II) oxide. The CLH report contains some data on other copper compounds (among which copper sulphate pentahydrate), from which the dossier submitter proposed to read-across to copper(II) oxide. In view of the considerations presented in the section "RAC general comment", RAC has not pursued the aspect of grouping any further. RAC concludes that in the absence of relevant data no proposal for classification for carcinogenicity can be made for copper(II) oxide.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal
No data on copper(II) oxide are available in the CLH report. However, in light of the proposal to read-across between the different copper compounds for systemic endpoints (see section "RAC general comment" above), the dossier submitter included in the CLH report several animal studies investigating the reproductive toxicity of other copper compounds, as well as some human data.

Fertility – Effects of copper sulphate pentahydrate on fertility were examined in a 2-generation study conducted according to OECD TG 416 (Mylchreest, 2005). No treatment-related effects were seen on any of the fertility and litter parameters investigated. Two other non GLP studies conducted with copper gluconate (De la Iglesia *et al.*, 1973) and copper sulphate (Lecyk, 1980), included as supporting evidence, also showed no effects on fertility.
Development – An OECD TG 414 compliant rabbit developmental toxicity study conducted with copper dihydroxide (Munley, 2003d) showed some slightly increased incidences in common skeletal variants that were considered secondary non-specific consequences of maternal toxicity. Two other non-guideline studies exposing rats and mice to copper gluconate via gavage (De la Iglesia *et al.*, 1972) did not reveal treatment-related effects on developmental parameters. Another non-guideline compliant study with copper acetate administered to rats via drinking water (Haddad *et al.*, 1991) showed some delayed ossification in foetuses but not in new-borns. In addition, two studies exposing pregnant rats, rabbits and hamsters to intra-uterine copper wire (to mimic exposure to intra-uterine contraceptive device (IUD)) showed no teratogenic or growth-retarding effects in the offspring (Barlow *et al.*, 1981; Chang & Tatum, 1973).
Human exposure – Copper in the uterus (as IUD) is known to prevent implantation of the blastocyst, but once implantation takes place the foetus develops normally. The CLH report mentions that although two cases of anencephaly after use of IUD have been reported (Graham *et al.*, 1980), more recent reports indicated that IUD did not increase the risk of congenital abnormalities (Pasquale, 1996; Weissmann-Brenner *et al.*, 2007). No further details on any of these publications were however presented. Dietary exposure to copper does not appear to result in adverse effects on pregnancy, birth or growth and development (Ralph & McArdle, 2001).
Based on the available data and the weight of evidence, the dossier submitter concluded that no classification for reproductive and developmental effects is warranted for copper compounds, including copper(II) oxide.

Comments received during public consultation
No comments were received during the public consultation.

Assessment and comparison with the classification criteria
RAC notes that no data on copper thiocyanate are available. The CLH report contains data on other copper compounds (among which copper sulphate pentahydrate), from which the dossier submitter proposed to read-across to copper(II) oxide. In view of the considerations presented in the section "RAC general comment", RAC has not pursued the aspect of grouping any further. RAC concludes that in the absence of relevant data no proposal for classification for reproductive toxicity can be made for copper(II) oxide.

ENVIRONMENTAL HAZARD ASSESSMENT

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal
Copper(II) oxide does not have a current harmonised classification. The dossier submitter (DS) proposed to classify the substance as Aquatic Acute 1 (H400) with an acute M-factor of 10 and as Aquatic Chronic 1 (H410) with a chronic M-factor of 1. The DS's proposal was based on the following arguments:

The water solubility of copper(II) oxide is equal to 0.394 mg/L and 0.01 mg/L at pH 6 and 9, respectively. Taking into account the recommendations of the CLP guidance[1], this compound is considered to be a readily soluble metal compound for classification purposes.

For aquatic acute classification, the lowest acute Ecotoxicity Reference Value (acute ERV_{CuO} 0.036 mg/L) was considered to be below the trigger value of 1 mg/L, the DS concluded the classification as Aquatic Acute 1 (H400) is appropiate.

As the lowest acute ERV_{CuO} (0.036 mg/L) is above 0.01 mg/L but ≤0.1 mg/L, the DS proposed an acute M-factor of 10.

In order to demonstrate removal from the water column (>70% removal within 28 days) to assess the "persistence" or lack of degradation of metal ions the DS considered information provided by the copper task force (Rader, 2013). Evidence of rapid removal from the water column was based on the TICKET-Unit World Model (UWM), which describes partitioning to dissolved organic carbon, particulates, etc., deposition and transformation to sulfides in sediment. Together with evidence from field studies, the dossier submitter considered that this provides a satisfactory description of copper ion dynamics, and was therefore of the opinion that more than 70% of dissolved copper (II) ions are removed from the water column within 28 days, i.e. that dissolved copper compounds are rapidly removed. The potential for copper remobilisation from sediment was expected to be limited in oxic and anoxic conditions.

For aquatic chronic classification, the DS proposed that rapid removal of copper(II) oxide from the water column can be demonstrated. The lowest chronic ERV_{CuO} (0.009 mg/L) was below the trigger value of 0.01 mg/L, hence the DS concluded that classification as Aquatic Chronic 1 (H410) is appropriate.

As the lowest chronic ERV_{CuO} (0.009 mg/L) is above 0.001 mg/L but ≤0.01 mg/L and the substance is subject to rapid removal, the DS proposed a chronic M-factor of 1.

Comments received during public consultation
Six comments were submitted on the environmental part of the proposal and none of the commenters agreed with the proposed classification. Five of them did not agree with the application of the rapid removal concept and subsequently proposed higher M-factors, and one commenter did not agree considering copper(II) oxide as fully soluble and as a consequence proposed a less stringent chronic classification and M-factor.

An industry association pointed to disagreements in the selection and interpretation of ecotoxicity data between the CLH report and the REACH dossier. While there was agreement with the DS's proposal on the acute classification it was suggested to classify copper(II) oxide as Aquatic Chronic 2 based on the use of a different chronic toxicity value resulting in a different chronic ERV_{CuO}. Four MSCAs objected to the use of the TICKET-UWM, for several reasons. Among them the fact that the model is designed for shallow lakes (so is not representative of turbulent or flowing systems or circumstances where sediment is not present), it includes significant assumptions about transformation to sulfides, and uses default assumptions for factors (like concentration of the particulate matter) that may vary spatially and temporally. One MSCA

[1] ECHA Guidance on the Application of the CLP criteria (version 4.0 November 2013)

pointed out that dissolution data for copper(II) oxide (CuO) show an increase in dissolved copper ion concentrations by a factor of four between day 7 and day 28 at a loading rate of 1 mg/L, which does not suggest rapid transformation to less soluble forms. The lack of an existing international agreement about how to apply the rapid removal concept was also highlighted (including by one other CA, although they did not object to the approach taken). These four CAs therefore indicated that dissolved copper (II) ions should not be considered to be rapidly removed from the aquatic environment, and that the proposed chronic M-factor should therefore be 10 rather than 1. In response, the dossier submitter agreed that copper (II) ions cannot currently be considered to be rapidly removed from the water column, and suggested changes to the proposed classification accordingly.

In addition, in several comments, MS requested changes to, or better justification of, the selection of the lowest ecotoxicity data values, since there appeared to be discrepancies between some of the source documents and the way the information was summarised in the CLH report. Some of the differences were related to the use of geometric means rather than the lowest value for a species, and in other cases it was due to uncertainties about whether the cited data referred to the compound itself or to the metal ion. Furthermore one CA pointed out that it may be appropriate to apply the surrogate approach, since there is no chronic test result available for the most sensitive species (*Pimephales promelas*) in the acute tests. In addition, the same CA noted that there are data on other invertebrate species and it was not clear why these were not included in the CLH report. Moreover, considering the amount of ecotoxicological data available for copper, it was proposed to use the species sensitivity distribution (SSD) curve for each trophic level for both short and long-term effects.

Another MSCA suggested that an explicit statement should be included that nano-forms should be considered separately.

Assessment and comparison with the classification criteria

Water solubility:
The CLH report does not present transformation/dissolution data for CuO over different timescales, pH values or loading rates. Copper(II) oxide is considered by the DS readily soluble based on water solubility values 0.394 mg/l and 0.01 mg/l at pH 6 and pH 9, respectively, being greater than the acute ERV of the dissolved metal ion concentration (acute ERV 0.292 mg Cu/L at pH 5.5 to 6.5).

RAC notes that transformation/dissolution (T/D) data exist according to the industry comments submitted during public consultation. These T/D data are considered by RAC in support to the conclusion drawn from the solubility data presented in the CLH report.

Degradability
Rapid removal: RAC considers that the TICKET-UWM provides a useful insight into key fate pathways for metal ions including copper in a model shallow lake system. This generic approach allows systematic comparisons to be made between metals. However, the choice of model default parameters has not (yet) been resolved, especially as some properties are likely to vary spatially and temporally. For example, comparison with monitoring data in the CLH report suggested that the model may overestimate the extent to which copper binds to particles, and may use a settling velocity that is higher than observed in reality. In addition, post-loading simulations for one field study that was claimed to be "more representative of a worst case scenario" (on the basis of settling velocity, distribution coefficient and a relatively low suspended solids concentration compared to model defaults) did not predict 70% removal from the water column after 28 days. As this was a natural lake, RAC does not agree that it should be dismissed as a "worst case". Since the concept of rapid degradation for organic substances is conservative and does not include sequestration by particulate matter (or other fate pathways such as volatility), it seems inconsistent to apply such approaches to metals.

The DS's proposal also relied heavily on the premise that copper (II) ions will partition rapidly to sediment, where they will be transformed at the surface to insoluble minerals (especially copper (II) sulfide) over a relatively short timescale so that binding to sediment is effectively irreversible.

RAC notes that the DS's proposal did not describe the behaviour of copper (II) ions in aquatic systems with little or no sediment (e.g. rivers or lakes with sand or gravel substrates), high turbulence or sediment at depths substantially in excess of 3 metres. Even where sediment is present, the oxidation state of surface layers may not always favour sulfide formation, and the situation may also be complicated if there is a high level of existing metal contamination. RAC therefore does not consider that a convincing case has been made that copper (II) ions will always rapidly speciate to non-available forms, or that this process was demonstrated to be irreversible under all relevant circumstances. At a general level, RAC considers that decisions about rapid removal could be based on observations from a standardised OECD Transformation/ Dissolution test. In this case, T/D studies showed increasing concentrations of copper ions over 28 days (not a decline), indicating that copper (II) ions remained in solution under these test conditions.

In conclusion, RAC considers that copper (II) ions are not subject to rapid environmental transformation for the purposes of classification and labelling.

Bioaccumulation

The bioaccumulation behaviour of copper (II) ions in organisms should consider both essentiality and homeostatic mechanisms. The DS's proposal did not present a clear description of the available data for comparison with the CLP criteria. However, in view of the degradability conclusion, this end-point does not influence the determination of the chronic M-factor and so was not considered further.

Ecotoxicity

Choice of ecotoxicity data: The ecotoxicity database for copper (II) ions is extensive, with many studies of acute and chronic toxicity in fish, invertebrates and algae/higher plants using a variety of copper compounds at different pH values as well as hardness and dissolved organic carbon (DOC) levels. The two principal sources of information cited in the DS's proposal are the pesticide DAR and the vRAR (2008). RAC considers that the chronic ecotoxicity information in the vRAR is generally reliable for hazard assessment as it was evaluated in depth by the relevant industry experts and reviewed by the pre-REACH CAs[1]. However, Tables 1-3 in Annex 1 (under section "Additional key elements") show that the presentation of ecotoxicity information in these sources is inconsistent (presumably due to differences in data aggregation as pointed out in the public comments). This is considered further below:

a) Given the large number of studies for individual species, the data in the CLH report were aggregated to present single values for each species in three different pH bands. The CLP Guidance for metals recommends transformation/dissolution testing at different pHs, so RAC agrees that grouping into pH bands is appropriate as there is a clear trend in toxicity that would be overlooked if all the data for a species were combined. However, the reasons for the choice of the actual pH bands were not explained, and the effects of hardness and DOC were not discussed.

b) The dossier submitter's proposal used geometric means even if there are only two data points for a species in a particular pH band. This is not consistent with the CLP Guidance (which indicates that at least four data points are preferred) or the REACH CSRs, and led to discrepancies between the data sets, which were noted during public consultation.

c) For invertebrates, data were presented for only two species of crustacean (*Daphnia magna* and *Ceriodaphnia dubia*). RAC notes that it is standard practice to consider all relevant data from reliable standard test guideline studies, and so the dossier submitter's proposal was not necessarily based on a comprehensive data set. The dossier submitter did not provide any additional information in response to the public

[1] Italy has been acting as a reviewing Member State for the substance and the risk assessment report has been reviewed by the Technical Committee on New and Existing Substances (TC NES) according to standard operational procedures of the Committee.

consultation comments on this issue. However, RAC notes that the vRAR (2008) contains long-term toxicity data for several other invertebrate taxonomic groups (including molluscs and insects) as well as higher plants (*Lemna minor*). Further details are provided in Annex 1 under section "Additional key elements".

i) In the vRAR (2008), all the reliable chronic NOEC data were compiled in a species sensitivity distribution, deriving a hazardous concentration for 5% of the species (HC_5) (with the 50th percentile confidence interval) of 7.3 µg/L (6.1-7.9 µg/L) based on the best fitting approach, or 6.1 µg/L (3.7-8.6 µg/L) using the log normal curve fitting. These values are very similar to the lowest NOEC in the dataset (6.0 µg/L for the mollusc *Juga plicifera*).

ii) Due to the variation in physico-chemical conditions used in the tests, in the vRAR (2008) the data were also 'normalised' using a biotic ligand model. The lowest normalised NOEC is 5.3 µg/L for the rotifer *Brachionus calyciflorus* (at pH 8.1, hardness of 165 mg/L $CaCO_3$ and DOC of 3.2 mg/L). The lowest HC_5-50 derived for an ecoregion is 7.8 µg/L (4.4-11.7 µg/L).

iii) RAC notes that the CLH report also mentioned a NOEC of 3.12 µg/L (as copper) from an indoor microcosm study using copper hydroxide, without specifying the measured end-point or study duration; it was also pointed out, in comments during the public consultation, that in the final EFSA conclusion a NOEC of 4.8 µg/L is cited which was used for the overall risk assessment for aquatic organisms. As it was not clear how this information would be used in hazard classification, it was not considered further.

In summary, the lowest long-term NOEC reported in the CLH report is 7.4 µg/L for *Ceriodaphnia dubia* at pH 6.5-7.5. The omission of data for other invertebrate groups from the DS's proposal does not appear to make a significant difference as the most sensitive data all lie in the range 1-10 µg/L.

Discrepancies in the ecotoxicity data as presented: The lowest acute toxicity value selected in the CLH report was 0.029 mg/L (29 µg/L) at pH 5.5-6.5, giving the source as the vRAR. The origin of this data point is unclear, but RAC assumes that it relates to data for *O. mykiss* (a similar value was obtained with *Ceriodaphnia dubia* at pH >7.5-8.5). The lowest geometric mean LC_{50} reported in the CLH report is 8.1 µg/L (as copper) for fathead minnow *P. promelas* at pH 5.5-6.5 (cited as coming from the vRAR – an actual study reference was not provided). This is based on two values, both for larval fish, 15.0 µg/L and 4.4 µg/L. During PC, industry indicated that the test medium in the study which resulted in the lowest EC_{50} (cited as Erickson *et al.,* 1996) used a high flow-through rate, had low hardness (22 mg $CaCO_3$/L) and low DOC concentration (not stated), and used larvae that were less than 24 hours' old. Although not mentioned in the CLH report, in the original paper the lowest LC_{50} was determined at the minimum pH, i.e. 6.0. Industry therefore considered this test to represent a worst case, and suggested that the sensitivity of this species at pH 6 versus pH 7 was unexpected and may be related to insufficient adaptation to low pH conditions. The data were therefore not considered reliable and not used for classification in the REACH registrations as well as the vRAR. Nevertheless, RAC notes that other minimum acute fish LC_{50}s are of the same order of magnitude (e.g. *O. mykiss* at all pHs, and *P. promelas* at pH 6.5-7.5). The OECD TG 203 permits testing in waters with total hardness as low as 10 mg $CaCO_3$/L, and a preferred minimum pH of 6.0, so the conditions used in the Erickson (1996) study were within the validity criteria of the guidelines and cannot be considered a worst case. In addition, this species can tolerate poor conditions such as turbid, hot, poorly oxygenated, intermittent streams, which are unsuitable for most fishes (http://www.fishbase.org/Summary/speciesSummary.php?ID=4785&AT=fathead+minnow).

Further papers provided by industry stakeholders following public consultation (Mount, 1973 and Zischke *et al.*, 1983) indicate that *P. promelas* can survive at pHs as low as 4.5, so that a pH of 6.0 does not appear to be intolerable over short exposures. RAC also notes that the replacement test for acute fish toxicity (OECD TG 236) involves embryos, so the life stage argument was not considered relevant either. It is also unclear why the dossier submitter decided to include them in the CLH report if they had been previously rejected. RAC accepts that an acute toxicity test with

fish larvae may be more sensitive than one with older fish if they were not properly acclimated, but does not find the other reasons for rejection convincing.

Data for other species show a trend of increasing acute fish toxicity with declining pH, presumably due to increasing bioavailability. The acute LC_{50} for *Danio rerio* at pH 6.5-7.5 (35 µg/L, n=3 so a geometric mean is not appropriate) is similar to that of *O. mykiss* at pH 5.5-6.5 (geometric mean 29 µg/L), implying that the sensitivity of *D. rerio* at the lower pH could be higher. Rather than ignoring the *P. promelas* data completely, the geometric mean LC_{50} of 8.1 µg/L is therefore considered to be relevant for hazard classification as it takes account of uncertainties about the sensitivity of fish at acidic pH, although this is a conservative approach given the life stages that were tested (N.B. if the most sensitive value of 4.4 µg/L were used the classification and acute M-factor would be the same for copper(II) oxide). RAC has not considered how DOC or hardness affect the observed pattern in ecotoxicity data, as such an analysis was not presented in the CLH report.

As noted above, the lowest reported long-term NOEC in the CLH report is 7.4 µg/L for *Ceriodaphnia dubia* at pH 6.5-7.5, and this value is consistent with the large amount of chronic data presented in the vRAR (2008), including the HC_5. However, this is almost identical to the acute LC_{50} for *P. promelas* at pH 5.5-6.5, and there are no measured chronic toxicity data for any fish species in the pH range of 5.5-6.5. Consequently, the adequancy of the long-term study results was questioned. At first sight it might seem disproportionate to consider the whole long-term fish toxicity data set (n=29) as 'non-adequate'. However, the acute fish test data clearly show that for the three species for which data across the total pH range of 5.5-8.5 are available, the toxicity is the highest in the lowest pH range, i.e. 5.5-6.5. Therefore, despite the large number of fish studies used in the dossier submitter's proposal, RAC believes that it is appropriate to consider the surrogate method for the fish trophic group (as was suggested in one of the public consultation comments). [N.B. The CLP criteria and guidance do not address this specific issue, but Example D in Section 4.1.3.4.4 of the CLP guidance is comparable to some extent. It describes a substance with a large data set, for which acute as well as chronic toxicity data are available for all three trophic levels. For crustacea, chronic data are available for *Daphnia magna*, which is clearly the least sensitive of the invertebrate species for which acute data are available. Hence, according to the guidance, the chronic aquatic toxicity data for *D. magna* in this case should be considered not in conformity with the definition of 'adequate chronic data'.]

In addition, it was noted in comments received during the public consultation that in the biocide Assessment Report for copper (II) hydroxide (Product type 8, RMS France, September 2011) the lowest reported NOEC is 2.2 µg Cu/L for growth in the fish *Oncorhynchus mykiss*. This appears to be aggregated in the CLH report with three other studies for this species in the pH 6.5-7.5 band, so that the geometric mean is 16.1 µg/L. RAC considers that this is acceptable, although as noted above, it does appear that some fish studies provide acute LC_{50}s in the range 1-10 µg/L. Similarly, it was indicated in comments received during public consultation that in the DAR for copper hydroxide, a 92-d NOEC of 1.7 µg/L was obtained in a fish early life stage test for *O. mykiss* at pH 8.0 (cited as Schäfers, 2000). This result does not appear to have been taken into account in the data aggregation used in the dossier submitter's proposal. A third reliable chronic result for this species in the pH range >7.5-8.5 was included in the CLH report (NOEC 16 µg Cu/L). Comments by industry following the public consultation raised some issues about the reliability of the lower value of 1.7 µg/L (e.g. the reported copper concentrations were highly variable in this study and the test substance was a formulation containing 10% w/w dispersant and also an adhesive). Whilst toxicity is still likely to have been driven by copper ions, the composition might have had some influence. It is also sparingly soluble, rather than a soluble salt. This result is therefore not used directly but is considered by RAC as supporting information for chronic classification purposes.

ERV derivation: **The lowest acute LC_{50}** (as dissolved copper) presented in the CLH report is 8.1 µg/L for *P. promelas* at pH 5.5–6.5. The acute ERV for CuO is therefore equal to 0.010 mg/L [{acute ERV of metal ion x molecular weight of the metal compound/(atomic weight of the metal x number of metal ions)}, so 0.0081 x 79.55/(63.55 x 1)]. This is lower than the acute ERV proposed in the CLH report (0.036 mg/L), which is based on a different acute toxicity value.

The lowest long-term NOEC (as dissolved copper) presented in the CLH dossier is 7.4 µg/L for *Ceriodaphnia dubia* at pH 6.5–7.5. The chronic ERV for CuO is equal to 0.009 mg/L [{chronic ERV

of metal ion x molecular weight of the metal compound/(atomic weight of the metal x number of metal ions)}, so 0.0074 x 79.55/(63.55 x 1)]. As noted in Annex 1, other apparently reliable NOEC data exist that are lower than this value, but still in the range 1-10 µg/L (e.g. a normalised NOEC of 5.3 µg/L for the rotifer *Brachionus calyciflorus* at pH 8.1, hardness of 165 mg/L $CaCO_3$ and DOC of 3.2 mg/L). They will therefore make only a very small difference to the chronic ERV. However, there are no chronic toxicity data for the fish species that is acutely most sensitive at pH 5.5-6.5, so the surrogate method for the fish trophic group is therefore considered.

Comments received during public consultation on related substances dicopper oxide, Bordeaux mixture and copper dihydroxide specifically suggested that the 92-d NOEC of 1.7 µg Cu/L for *O. mykiss* (obtained with copper hydroxide) should be used as the basis for the chronic classification. As already noted, this value is the same order of magnitude as the other sensitive chronic data, but it would not impact the chronic ERV of 0.0081 mg/L. RAC notes that this result was obtained at pH 8, for which only one other value is available for this species in that pH range. Since aquatic toxicity appears to generally increase as the pH is lowered, the implication is that the selected chronic data set might not be sufficiently sensitive. This value is therefore considered alongside the surrogate method.

Acute aquatic hazard:
The water solubility (0.394 mg/L at pH 6 and 0.01 mg/L at pH 9) exceeds the acute ERV of the dissolved metal ion (0.0081 mg Cu/L based on the *P. promelas* data), so the substance is considered to be a readily soluble metal compound. RAC agrees to classify copper(II) oxide as **Aquatic Acute 1 (H400)** on the basis of the acute ERV_{CuO} (0.010 mg/L). As the acute ERV_{CuO} is above 0.001 mg/L but ≤0.01 mg/L, the **acute M-factor is 100**.

Chronic aquatic hazard:
As the substance is considered to be a readily soluble metal compound, classification may be based on the chronic ERV_{CuO} (0.009 mg/L). Since this is below 0.1 mg/L, classification as **Aquatic Chronic 1 (H410)** is appropriate for a substance not subject to rapid environmental transformation, based on RAC conclusion on rapid removal from the environment. As the lowest chronic ERV_{CuO} is above 0.001 mg/L but ≤0.01 mg/L, the chronic M-factor would be 10 for a substance not subject to rapid environmental transformation. However, using the surrogate method for the fish trophic group, the **chronic M-factor** should be consistent with the acute M-factor, i.e. **100**.

In summary, RAC agrees with the proposal to classify dicopper oxide as **Aquatic Acute 1 (H400**) and **Aquatic Chronic 1 (H410)**, but considers that the proposed acute and chronic **M-factors** should be **100** because of the conclusion on rapid environmental transformation as well as the most sensitive fish toxicity data. The classification is based on a MW of 79.55 and the presence of 1 copper atom per molecule.

Additional references

European Copper Institute 2008. Appendix K1 in Voluntary Risk Assessment of copper, copper II sulphate pentahydrate, copper(I)oxide, copper(II)oxide, dicopper chloride trihydroxide. European Copper Institute (ECI). Available at (19/09/2014): http://echa.europa.eu/fi/copper-voluntary-risk-assessment-reports/-/substance/474/search/+/term

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Zischke, J.A., Arthur J.W., Nordlie K.J., Hermanutz R.O., Standen D.A., and Henry T.P. (1983). Acidification effects on macroinvertebrates and fathead minnows (*Pimephales promelas*) in outdoor experimental channels. Water Research, 17, 47- 63.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and by RAC (excl. confidential information).