Committee for Risk Assessment

RAC

Opinion
proposing harmonised classification and labelling at EU level of

Granulated copper

EC Number: 231-159-6
CAS Number: 7440-50-8

CLH-O-0000001412-86-216/F

Adopted

8 June 2018

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8 June 2018

CLH-O-0000001412-86-216/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:

Chemical name: Granulated copper

EC Number: 231-159-6

CAS Number: 7440-50-8

The proposal was submitted by France and received by RAC on 13 February 2017.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

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 4 April 2017. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by 19 May 2017.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: Steven 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 and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on 8 June 2018 by consensus.

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 and ATE	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	No current Annex VI entry										
Dossier submitters proposal	TBD	Granulated copper	231-159-6	7440-50-8	Eye Irrit. 2 Aquatic Chronic 2	H319 H411	GHS07 GHS09	H319 H411			
RAC opinion	TBD	Granulated copper	231-159-6	7440-50-8	Aquatic Chronic 2	H411	GHS09	H411			#
Resulting Annex VI entry if agreed by COM	TBD	Granulated copper	231-159-6	7440-50-8	Aquatic Chronic 2	H411	GHS09	H411			#

RAC recommends a note be included, which defines the size of granules

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Granulated copper is a form of copper metal defined by its particle size and specific surface area. In the CLP guidance, the default diameter for massive metal is 1 mm. If the diameter of a sphere for massive copper is > 1 mm, the corresponding surface area is < 0.67 mm^2/mg (<6.74 cm^2/g). However, granulated copper particles are cylindrical with a length greater than 1 mm (range: 0.9 – 6.0 mm; mean: 2.1 mm) and width below 1 mm (range: 0.494 – 0.949 mm; mean: 0.706 mm), and a surface area of 25.6 cm^2/g (significantly above the limit for massive). As such, it is considered to be between massive (defined as a sphere with a diameter >1 mm and a surface area of <6.74 cm^2/g) and the powder form (diameter of <0.2 mm and a surface area of 240 cm^2/g) of copper.

RAC previously evaluated CLH proposals for ten other copper compounds from the same dossier submitter (DS) (France). For these copper compounds, as well as now for granulated copper, the dossier submitter stated that where systemic toxicity is concerned, 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 (such as granulated copper). For the assessment of the systemic endpoints, with no data available on granulated copper itself, the dossier submitter therefore proposed to read-across from data on the different copper compounds previously evaluated. The present CLH report is thus similar to the other ten copper compounds for STOT RE, germ cell mutagenicity, carcinogenicity and reproductive toxicity. The test substance in studies reported in these common sections is most often copper sulphate pentahydrate, but sometimes also other copper compounds have been tested.

RAC previously considered the dossier submitter's proposal to group the information on copper containing substances together for consideration of STOT RE and the CMR endpoints. RAC noted then 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 on the ten copper compounds, whereas RAC concluded that these would need a more detailed analysis. But as none of the studies with copper sulphate pentahydrate or the other tested copper substances yielded positive evidence for the classification for these endpoints, RAC at that time did not pursue the aspect of grouping the copper containing substances any further. For the present evaluation of granulated copper, RAC maintains this position, whilst noting that for granulated copper (with no anion present) only toxicity of the Cu^{2+} ion is relevant.

For the assessment of the local and acute human health endpoints (acute toxicity, STOT SE, skin irritation/corrosion, eye damage/irritation and skin sensitisation), the dossier submitter proposed to read-across from the data on the previously evaluated coated copper flakes, in combination with a comparative analysis of particle and solubility characteristics. With granulated copper being a particle with the aforementioned defined size, it was argued that copper massive, copper powder and coated copper flakes are the most representative forms for extrapolation. Since toxicity data are only available for coated copper flakes, read-across from this substance was proposed. RAC's considerations on this read-across in combination with the comparative analysis are presented in the respective local and acute endpoint sections.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

Granulated copper is a stable inorganic compound. Based on the chemical composition and experience in use, the dossier submitter does not expect granulated copper to have flammable, explosive or oxidising properties. Moreover, granulated copper is indicated to be thermally stable up to 1000 °C. The dossier submitter therefore proposed no classification for physical hazards.

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC supports no-classification for physical hazards, as proposed by the dossier submitter.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

In the absence of acute toxicity data for granulated copper, the dossier submitter used data available on the acute oral and dermal toxicity of coated copper flakes (Sanders 2001a/b) in combination with comparative physico-chemical data (particle size and surface area, solubility) to arrive at a proposal for no classification for all three routes of administration.

In an *in vitro* bio-elution assay (Rodriguez *et al.*, 2010), copper compounds (copper sulphate, copper wire, copper oxide, cuprous chloride, coated biocidal and non-biocidal copper flakes, and copper powder) were tested for their potential to release bioaccessible metal to artificial gastric juice. A two hour test was performed at pH 1.5, using 2 g/L and 200 mg/L sample loading. The test was carried out in HCl 0.07N with an agitation rate of 171 rpm, at 37 °C in darkness. The samples were agitated for 1 hour and left to stand for another hour. The results (expressed as % mass recovered at the end of the bio-elution test as compared to the results obtained for soluble copper sulphate) and the physico-chemical parameters of the tested copper compounds are presented in the table below.

Table. Bio-elution of copper compounds (Rodriguez et al., 2010)

Material Tested	Composition	Particle size	Surface area	Bio-elution recovery (as % of Cu content)	
				200 mg/L loading	2 g/L loading
Copper wire massive	>99.9% Cu	0.13(a), 0.4(b), 1(c) mm	<6.74 cm^2/g		0.096-0.105
Copper powder	99.7% Cu, 0.3% Cu_2O	0.1-0.2 mm	240 cm^2/g	1.1	7*
Coated copper flakes	93.7% Cu, 2.6% Cu_2O, 3.89% LOI**	0.008-0.01 mm	29000 cm^2/g	60-71	42-44

Copper chloride		n/a	n/a	77	94
Copper oxide		n/a	n/a	84	68
Copper sulphate	25.45% Cu	n/a	n/a		100
Granulated Copper	>99% Cu	1.086 mm	25.6 cm^2/g		

*The results at the higher loading rate show unacceptably high variability (CV of 66%), possibly related to abrasion of the particles during the test. The results of this test are therefore not considered as reliable. ** Loss on ignition, as a measure of the organic content.

According to the dossier submitter, granulated copper (diameter: 1.086 mm; specific area of 25.6 cm^2/g) assessed in this dossier could be considered in the range of massive wire and powder copper (with relative biosolubilities of 0.1 and 1.1%, respectively), less so in the range of coated copper flakes. However, as data are available on coated copper flakes but not on massive or powder copper, read-across from coated copper flakes is proposed, acknowledging that this would represent a worst-case for granulated copper, given the relatively high biosolubility of coated copper flakes.

The CLH report included two acute toxicity studies with coated copper flakes in rats. In an oral study, conducted according to OECD TG 423, the LD_{50} value for males and females combined was estimated to be between 300 and 500 mg/kg bw (Sanders, 2001d), resulting in classification as Acute Tox. 4; H302 for coated copper flakes. In a dermal study, conducted according to OECD TG 402, no mortalities were seen, resulting in an LD_{50} value >2000 mg/kg bw (Sanders, 2001b) and thus no classification for coated copper flakes (dermal route).

In view of the much lower biosolubility in gastric fluids of copper powder, massive and (presumably) granulates compared to coated copper flakes, no classification is proposed for granulated copper in contrast with the coated copper flakes. In support of the 'no classification', the dossier submitter presented acute toxicity data for other forms of copper, expressed as "biosoluble" copper (see the table below).

Table. Acute toxicity of copper compounds, expressed as external doses of substance and calculated as internal dose, using the biosolubility data from Table 1

Source material tested	LD_{50} (mg substance/ kg bw)	Cu Biosolubility (%)	LD_{50} as biosoluble Cu (mg Cu/kg bw)
Cu flakes; 98% Cu	300 – 500 (0.005 mm)	42 – 71 (0.0085 mm)	231 (121 – 341) (0.005 mm)
$CuSO_4$; 25.4% Cu	481	100	123
CuCl; 63.78% Cu	336	77 – 94	144 - 201

A linear relationship was observed in the Rodriguez *et al.* (2010) study when plotting the bio-elution against the surface area for the three sizes of copper wire tested. Extrapolation to 1.086 mm (the surface area of granulated copper) indicates a bio-elution of 6-17% is at least required (granulated copper consists for over 99% of copper) to reach sufficient Cu^{2+} concentrations that would cause effects warranting classification for Acute Tox. 4. Since the estimated surface area of granulated copper is somewhere between copper powder and massive copper forms, the bio-elution is expected to be small, between 0.1 and 1.1%. Therefore no effects are expected that warrant classification for acute oral toxicity.

For the dermal route, the dossier submitter concluded that no classification for granulated copper is warranted, given that coated copper flakes are not classified for acute dermal toxicity, nor in fact are any of the other previously evaluated copper compounds.

For the inhalation route, read-across to coated copper flakes was not applied, given that in contrast to coated copper flakes granulated copper is not available as inhalable particles (with average particle size significantly >0.100 mm) and is non-bioavailable. Therefore no classification by the inhalation route is proposed contrary to coated copper flakes (classified as Acute Tox. 3; H332).

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC notes that no acute toxicity data are available specifically for granulated copper. The CLH report contains acute toxicity data on coated copper flakes, from which the dossier submitter proposed to read-across to granulated copper for the oral and dermal route. Additionally, supporting information was provided for the read-across argumentation that is focused around particle size, surface area and solubility characteristics of various copper compounds.

The information provided in the bio-elution test with artificial gastric juice suggests that the bio-elution of granulated copper will be very small upon oral administration, leading to a bioavailability that is likely too small to illicit effects that warrant classification for acute oral toxicity. The bio-elution characteristics of granulated copper supposedly lie somewhere between copper powder and copper wire (massive) in terms of particle size and surface area. This seems to be supported by an apparent linear relation between surface area and the bio-elution of the different sizes of copper massive tested. Whereas copper powder, copper wire and copper flakes are forms of copper without counter ions that could affect the biosolubility, RAC considers it plausible that the bio-elution of granulated copper is more in the range of copper powder and copper wire than in the range of copper flakes (much smaller particles and unknown effect of coating on bio-elution). Yet, RAC notes the ongoing debate on the applicability of the bio-elution concept, without internationally agreed guidelines for the conduct of bio-elution techniques/studies available at the moment and without data to show a systematic relationship between bio-elution and systemic availability. RAC notes some further uncertainties as to the current study. For instance, the bio-elution measured for the various copper compounds is based on an *in vitro* test simulating bioavailability in the stomach only. Therefore there is an underlying assumption that the bio-elution ratio (difference) between copper compounds tested in *in vitro* gastric fluid is similar in comparison to bio-elution *in vivo* passing through several organs/tissues. Additionally, the *in vitro* bio-elution was performed during one hour agitation plus one hour static while *in vivo* the agitation and timeframe might be different. RAC finally notes that the comparison between biosolubility and acute toxicity/LD_{50} data was only done for highly (bio)soluble copper compounds, not for the much less (bio)soluble copper powder/copper massive. No data were thus presented showing that copper compounds of more similar (bio)solubility to granulated copper have an LD_{50} value above the cut-off of 2000 mg/kg bw for classification. RAC concludes that in the absence of sufficient data, no proposal for classification for acute oral toxicity can be made for granulated copper.

RAC notes that for acute dermal toxicity, the proposed read-across from coated copper flakes is hampered by the comparative biosolubility data being based on a bio-elution test using a fluid mimicking gastric juice rather than artificial sweat. RAC however also notes that none of the ten previously evaluated copper compounds was classified for acute dermal toxicity, not even the

most soluble one (copper sulphate pentahydrate). In view of this, RAC does not expect granulated copper to present this hazard and therefore supports the proposed no classification for acute dermal toxicity.

No read-across was proposed for acute inhalation toxicity because the particle size of granulated copper was considered too large for inhalation. Although the available particle size information provides no specific data regarding the fraction of inhalable particles present in granulated copper, based on the available granulometry indicating length ranges between 0.9 and 6.0 mm and width ranges between 0.494 and 0.949 mm, the presence of a substantial percentage of inhalable particles is considered unlikely. RAC therefore concurs with the DS that no classification for acute inhalation toxicity is warranted for granulated copper.

In summary, no classification is the RAC conclusion for acute toxicity of granulated copper via any route of administration.

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

Summary of the Dossier Submitter's proposal

The proposal for this endpoint is based on read-across from coated copper flakes as no data for granulated copper are available. The data for coated copper flakes is considered by the dossier submitter as a worst-case scenario for granulated copper because the solubility as an indicator for bioavailability is much higher, and toxicity is considered to be caused by the copper ion.

No clear evidence of specific target organ toxicity was reported in the acute toxicity studies with coated copper flakes. Clinical signs of toxicity were transient in nature and they were considered to be unspecific signs of general acute toxicity. Acute toxicity in humans is infrequent and generally results from ingestion of contaminated foodstuffs/beverages, for suicide purposes. As this led to no classification for STOT SE for coated copper flakes, the dossier submitter concluded that also no classification is warranted for granulated copper for STOT SE.

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC notes that no data are available for granulated copper. RAC however also notes that neither coated copper flakes nor any of the other nine previously evaluated copper compounds was classified for STOT SE. This was due to the fact that in the acute toxicity studies available for these copper compounds the effects observed were mostly general and transient in nature and not indicative of specific target organ toxicity, narcotic effects or respiratory tract irritation. Furthermore, in human self-poisoning cases with copper sulfate the most frequently observed symptoms (nausea, epigastric burning, vomiting, diarrhoea) were also indicative of non-specific, general acute toxicity. In view of this, RAC supports the proposed no classification for STOT SE for granulated copper.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The proposal for this endpoint is based on read-across from coated copper flakes as no data for granulated copper are available. The CLH report included one skin irritation study with rabbits, conducted with coated copper flakes according to OECD TG 404 (Sanders, 2001a). Since no erythema or oedema was observed in any animal at any time point, this study resulted in no classification for skin irritation for coated copper flakes. Considering the relatively high biosolubility of coated copper flakes compared to granulated copper, the dossier submitter considered coated copper flakes to represent a worst-case scenario for granulated copper. Because coated copper flakes were not classified for skin irritation, it was concluded that granulated copper does not need to be classified for skin irritation either.

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

No data are available for granulated copper. RAC notes that for skin irritation the proposed read-across from coated copper flakes is hampered by the comparative biosolubility data being based on a bio-elution test using a fluid mimicking gastric juice rather than artificial sweat. However, when looking at the skin irritation studies available for all ten previously evaluated copper compounds, RAC notes that none warranted classification, irrespective of the degree of solubility (a potential indicator of copper ion irritancy) of the copper compound tested. Given that not even the most soluble form (copper sulphate pentahydrate) was classified for skin irritation, RAC does not expect granulated copper to require classification either and therefore supports the proposed no classification of granulated copper for skin corrosion/irritation.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The proposal for this endpoint is based on read-across from coated copper flakes as no data for granulated copper are available. The CLH report included one eye irritation study with rabbits, conducted with coated copper flakes according to OECD TG 405 (Sanders, 2001c). Coated copper flakes caused signs of irritation in the available eye irritation study. All effects were shown to be reversible within 21 days. Whereas the mean scores over 24-72 h were below the threshold values for classification for iritis, conjunctival redness and chemosis (≥1, ≥2 and ≥2, respectively), the mean score for corneal opacity over 24-72 h was at or above the threshold value for classification (≥1) in 2 of the 3 tested animals. The mean score over all three animals (1) was also at this threshold value. Based on these results, coated copper flakes were classified with Eye Irrit. 2; H319. The same classification was proposed for granulated copper.

Comments received during public consultation

Industry, supported by a MSCA, indicated that due to the specific form of granulated copper, it is not suitable for testing in eye irritation studies. On the one hand, the substance is a very coarse material which on contact with the eye could be considered as a possible cause of physical trauma. On the other hand, it would quickly be physically removed by anyone exposed to the substance

because of its relatively large size. From that perspective, industry considered classification not warranted. With solubility being a potential indicator of copper ion irritancy, industry supported that for the purpose of classification, read-across based on solubility is possible with other copper compounds tested for eye irritation. Based however on a comparison of available transformation-dissolution data and results of eye irritation studies for (in descending order of copper release) copper sulphate pentahydrate (classified), coated copper flake (classified), dicopper oxide (classified) and copper oxide (not classified), they argued that for copper granulate, with an even lower release of copper than copper oxide, classification as an eye irritant is not warranted.

Assessment and comparison with the classification criteria

Given the specific form and particle size of granulated copper, RAC does not consider the proposed read-across from coated copper flakes appropriate and further notes that it is unclear whether the observed eye effects in the study with coated copper flakes were due to the particles causing mechanistic irritation or by dissolution of copper resulting in irritating effects. Also the contribution of the coating is unclear. RAC concludes that for granulated copper no proposal for classification for eye irritation can be made due to the absence of relevant data,. RAC acknowledges though that the testing of particulate solids for eye irritation may have issues related to physical stress.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

In the absence of data for granulated copper, the dossier submitter proposed to read-across from coated copper flakes. In the CLH report a guinea pig maximisation test (GPMT), conducted with coated copper flakes is included, as well as some human data.

In the GPMT test, conducted according to OECD TG 406, intradermal and topical induction doses of coated copper flakes were 0.1% (w/w) and 50% (w/w) at days 1 and 7, respectively (Sanders, 2001e). Animals were challenged with 25% (w/w) and 50% (w/w) at day 21. No reactions were seen in any of the tested (n=10) or control (n=5) animals.

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.

On the basis of the data above, coated copper flakes were concluded not to be skin sensitising, and were therefore not classified as such. Considering the relatively high potential biosolubility of coated copper flakes compared to granulated copper, the dossier submitter considered coated copper flakes to represent a worst-case for granulated copper, and concluded that granulated copper does not need to be classified for skin sensitisation either.

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC notes that for skin sensitisation the proposed read-across from coated copper flakes is hampered by the comparative biosolubility data being based on a bio-elution test using a fluid

mimicking gastric juice rather than artificial sweat. RAC however also notes that none of the ten previously evaluated copper compounds was classified for skin sensitisation, based on the results of skin sensitisation studies with these copper compounds, in combination with evidence for a very low skin skin sensitising potential of copper compounds in humans. In view of this, RAC supports the proposed no classification of granulated copper for skin sensitisation.

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

Summary of the Dossier Submitter's proposal

No data on granulated copper 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 were 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 which was conducted with dicopper oxide (Kirkpatrick, 2010) was included together with 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).

With regard to available human data, a human case study of chronic oral self-administration of copper causing liver failure (O'Donohue *et al.*, 1993) was reported together with human volunteer studies demonstrating nausea associated with copper sulphate in drinking water (Araya *et al.*, 2001, 2003). Human case studies of chronic inhalation exposure to Bordeaux Mixture causing pulmonary lesions were also reported (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 were 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.

Assessment and comparison with the classification criteria

RAC notes that no data on granulated copper 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 granulated copper. 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 for granulated copper, no proposal for classification for STOT-RE can be made due to the absence of relevant data.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter’s proposal

No data on granulated copper 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, 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 as well as a rec-assay with copper chloride were all reported as negative. 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, whereas 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 granulated copper.

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC notes that no data on granulated copper 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 granulated copper. 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 for granulated copper no proposal for classification for germ cell mutagenicity can be made due to the absence of relevant data.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter’s proposal

No data on granulated copper were provided 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 were 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 was 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 assessment in humans and animals concluded that copper is not carcinogenic and that therefore no classification for carcinogenicity is warranted for copper compounds, including granulated copper.

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC notes that no data on granulated copper 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 granulated copper. 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 for granulated copper no proposal for classification for carcinogenicity can be made due to the absence of relevant data.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

No data on granulated copper were provided 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 some human data, as well as several animal studies investigating the reproductive toxicity of other copper compounds.

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 assessment, the dossier submitter concluded that no classification for reproductive and developmental effects is warranted for copper compounds, including granulated copper.

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC notes that no data on granulated copper 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 granulated copper. 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 for granulated copper no proposal for classification for toxicity to reproduction can be made due to the absence of relevant data.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter’s proposal

Copper metal (massive, powder and granulated) is not currently listed in Annex VI of the CLP Regulation (EC) 1272/2008. The DS proposed that granulated copper does not require classification for Aquatic Acute hazard because the dissolved copper ion concentrations after a period of 7 days at a loading rate of 1 mg/L are below the acute ecotoxicological reference values (ERVs) of the dissolved form of copper, regardless of pH. It is, however, proposed to be classified as Aquatic Chronic 2 (H411) based on the dissolved metal ion concentrations after a period of 28 days at a loading rate of 1 mg/L, which are above the chronic ERVs at pH 6 and 7 (the estimated dissolved metal ion concentrations at a notional loading rate of 0.1 mg/L are below the chronic ERVs at pH 6, 7 and 8).

Degradation

The substance is an element and so is not degradable by definition. It is therefore not relevant to assess degradation rate as is usually done for organic compounds. However, copper is subject to chemical transformation processes and the vast majority of copper in aquatic systems is rapidly bound to particles, precipitated as insoluble inorganic salts, or bound to organic matter. In pure water, very low levels of free copper (II) ions are present in solution, with amounts governed by the propensity of the metal cation to hydrolyse in water. For a given mass of substance, the concentration of copper (II) ions in solution are highest at low pH (also depending on the type and concentration of ligands present in the water).

The DS summarises the previous RAC opinions for several copper compounds adopted in December 2014, which concluded that copper (II) ions are not subject to rapid environmental transformation for the purposes of classification and labelling. New evidence is available in the REACH registration dossier for copper (dated 18/01/2017), but as there is no new guidance available about the “rapid removal concept” for metal compounds, the data were not presented or discussed further.

Bioaccumulation

The DS refers to the previous RAC opinions on copper compounds adopted in December 2014, which conclude that the bioaccumulation behaviour of copper (II) ions is complicated by essentiality and homeostatic mechanisms in organisms, but does not need to be considered further because it does not influence the determination of the chronic M-factor (in view of the degradability conclusion).

Aquatic toxicity

The available database for copper (II) cations is large because several soluble (and less soluble) copper compounds have been tested under a wide range of abiotic conditions involving a variety of species. There are close to 800 acute and 200 chronic data points. Many of the studies are academic research papers rather than formal regulatory reports. The DS took account of the

information included in the REACH registration dossier for copper (dated 18/01/2017), which was based on existing regulatory reviews and two further reports (Heijerick and Van Sprang, 2016a & 2016b). The general approach is as follows:

- *Species selection and test duration*: Although data for many species are available, only the "standard" species and endpoints from standardised methods have been selected. For example, 96-h LC_{50} values for fish generated according to OECD TG 203 and OECD TG 236 have been used for acute classification. However, some exceptions were made. For example, acute but not chronic data were included for *Ceriodaphnia dubia* alongside *Daphnia magna* for the invertebrate trophic group; the argument being that the 7-d NOEC endpoint is not mentioned in the CLP Guidance and was 'rejected' in a Joint Research Centre (JRC) report on criteria for environmental long-term aquatic hazard classification [no further details are provided in the documentation, but following a request from the rapporteur, a copy of this report was provided and the statement about the use of *Ceriodaphnia* data appears to be based on a simplistic reading of the CLP Guidance; RAC notes that data for this species were also used in previous RAC opinions for other copper compounds]. On the other hand, test durations as low as 7 days were included in the chronic fish data set (*e.g.* a sub-chronic test with Fathead Minnow (*Pimephales promelas*) larvae by Norberg & Mount, 1985 [referred to as Nordberg *et al*. in the CLH dossier]).
- *Quality criteria*: Reported adverse effect levels must be expressed as measured, dissolved copper concentrations. Nominal data are not acceptable.
- *Physico-chemical conditions of test media*: Three factors were considered:
  - Data were split into three pH categories: 5.5-6.5, >6.5-7.5 and >7.5-8.5 to be in line with the UN GHS transformation/dissolution protocol (T/Dp), which specifies a pH range of 6-8.5 for the 7-day test and 5.5 to 8.5 for the 28-day test.
  - The effect of dissolved organic carbon (DOC) was taken account of by deriving ERVs based on both the whole data set and data normalised to a DOC level of 2 mg/L (which is the limit value in OECD TGs) where the data allow. The actual normalisation technique was not described. In addition, the OECD TGs recommend that 2 mg/L is a maximum limit for Total Organic Carbon (TOC) (the DOC level is not explicitly mentioned), and several studies had DOC levels much higher than this.
  - Water hardness does not influence the sensitivity of algae to copper, and reduces the acute sensitivity of invertebrates and fish; it has little influence on the chronic sensitivity of invertebrates but reduces the chronic sensitivity of fish. The median hardness of the media in the selected tests is generally in the lower end of the range of the OECD recommendations (10-250 mg $CaCO_3$/L) for each pH class. Therefore, the DS concluded that the ecotoxicity data are generally conservative with regards to the hardness of the test media.
- *Data aggregation*: The CLP Guidance (version 4.1, p. 500-501, Section 4.1.3.2.4.3) states that geometric means can be used if four or more equivalent data points are available for a species. The splitting of the data set according to pH reduces the overall number of data points for a species in any particular pH band. The REACH Registrants have argued that geometric means can still be used after splitting the database by pH band as long as at least four data points are available for the species across all pH values because this otherwise leads to "double" conservatism (i.e. if averaging is not applied, the lowest value within each pH band is selected due to data scarcity; this skews the data to the most sensitive value of all regardless of the mass of other information available for a species, and it should be born in mind that the hardness considerations may already introduce a

level of conservatism). To analyse the impact of the use of geomean or lowest value (if less than 4 data points are available) in a pH band, the DS presents both approaches.

The following description presents the available toxicity information for each trophic group, with the lowest values highlighted in bold.

Acute fish toxicity

Acute data are reported for five fish species, which becomes three species when the data are normalised for DOC (due to missing information for the other two species). The large majority of studies have been conducted in the highest (most alkaline) pH band, so data are only available for two fish species in the acidic pH band (5.5-6.5) at which toxicity is greatest, as outlined in the follwoing Table (see also Figure below).

Table : *Summary of acute LC_{50} data (µg/L) for fish at acidic pH normalised to a DOC level of 2 mg/L*

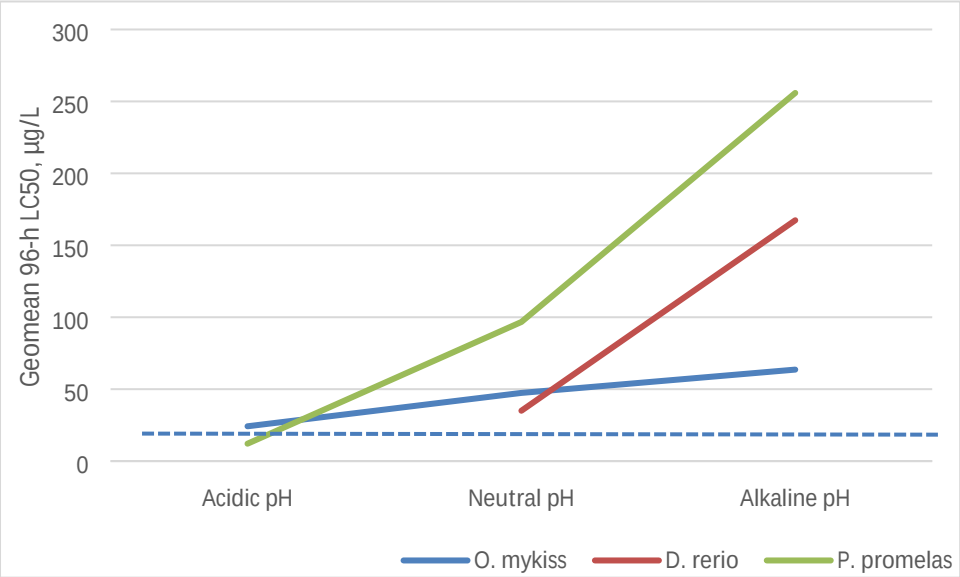
	Species	
	Oncorhynchus mykiss (Rainbow Trout)	*Pimephales promelas* (Fathead Minnow)
No. of values	8	3
Minimum	6.28	14.9
Maximum	99.3	40.1
Geometric mean	40.6	23.5[a]
Lowest value (when n<4)	-	14.9

Note: a - Less than 4 data points are available. However, two additional data points for *P. promelas* are available if DOC normalisation is not performed, so that a geometric mean that is compliant with the CLP Guidance can be derived (n>4). In the previous RAC opinions for other copper compounds, the lowest LC_{50} was 8.1 µg/L for larval *P. promelas* at pH 5.5-6.5 from a single study (this was a geomean of two values – 15.0 and 4.4 µg/L). This study did not report DOC levels, so is not included in the Table, but it is part of the non-normalised data set. The geomean LC_{50} changes to 12.1 µg/L when all data for this species are included for this pH band.

For comparison, there are 69 additional acute data points for *Oncoryhnchus mykiss* and 253 for *P. promelas* in the two other pH bands (the geometric mean LC_{50} is in the range 10-100 µg/L for *O. mykiss* at both neutral and alkaline pH, whereas it is above 100 µg/L for *P. promelas* at alkaline pH). This demonstrates an unequal spread of data across pH bands (although it should be noted that for the majority of substances, there are typically only 1-3 acute fish studies covering all pHs).

When data are normalised for DOC, the third species (Zebrafish *Danio rerio*) has only two data points at pH >7.5-8.5 (alkaline) (LC_{50}: geometric mean 117.9 µg/L, lowest 94.7 µg/L) and one data point at pH >6.5–7.5 (neutral) (LC_{50}: 26 µg/L; the non-normalised LC_{50} is 11.7 µg/L). The lowest value was obtained in a very soft water test medium (hardness 7.8 mg/L as $CaCO_3$, which is outside the range of the OECD TG recommendation). This result is therefore highly conservative. In contrast, the studies at alkaline pH were performed using relatively hard waters (141 mg/L as $CaCO_3$). The use of a very soft water at neutral pH makes it difficult to compare sensitivities between species, and RAC considers that it is not relevant to use data obtained at hardness levels outside of the recommended range for hazard classification purposes. There is a second study at neutral pH that gave an LC_{50} of 35 µg/L (Bresch, 1982; this study used a reconstituted water with a hardness of 100 mg/L as $CaCO_3$ but DOC levels were not reported). When the trends between fish species are compared, as a worst case, it is possible that the LC_{50} for *D. rerio* might be below 10 µg/L at acidic pH (see Figure 1, prepared by RAC). This could be considered a data gap despite the large amount of data for acute fish toxicity. Zebrafish can be tested in waters down to pH 6 (OECD TG 203) or 6.5 (OECD TG 236) so it would be possible to perform a test to see if they are more sensitive.

Figure: Summary of acute LC_{50} data (µg/L) for fish (not normalised for DOC level, excluding data from very soft waters; dashed line = 10 µg/L)



Note: The slopes of the lines change if DOC normalisation is performed, though the general trends are still apparent.

To summarise, the lowest acute LC_{50} value for fish in the data set when not normalised for DOC is 12.1 **µg/L** (geomean for *P. promelas* at pH 5.5-6.5, n = 5). If geomeans are only used when there are ≥4 data points for a species in a pH band, the lowest fish LC_{50} would be 11.7 **µg/L** (for *D. rerio* at pH >6.5-7.5) [though as noted above, RAC does not think this is an appropriate data point as it was obtained in very soft water]. If DOC normalisation is performed, the lowest fish LC_{50} value is 14.9 **µg/L** (for *P. promelas* at pH 5.5-6.5, n = 3; the geomean is in the same concentration band, as indicated in the Table above). The hardness of the test media used to derive these values was in the range 22 - 48 mg/L as $CaCO_3$ for the *P. promelas* studies, and 100 mg/L as $CaCO_3$ for the *D. rerio* study. These reflect low hardness conditions and are therefore conservative. However, RAC notes that a lower LC_{50} (potentially below 10 µg/L) cannot be ruled out for *D. rerio* at pH 5.5-6.5.

Acute invertebrate toxicity

Over 300 individual acute data points are available for two "standard" aquatic invertebrate species (*Daphnia magna* and *Ceriodaphnia dubia*). There are more than 4 studies available for each pH band, with greatest sensitivity apparent at acidic pH. Geometric mean acute EC_{50} values at pH 5.5-6.5 are 16.3 µg/L (not normalised, n=29) and 11 µg/L (normalised for a DOC level of 2 mg/L, n=26) for *D. magna* and 12.6 µg/L (not normalised, n=9) and 16 µg/L (normalised for a DOC level of 2 mg/L, n=8) for *C. dubia.*

Acute algal/macrophyte toxicity

Over 50 individual acute data points are available for three "standard" algal species (*Pseudokirchneriella subcapitata* (n=36), *Chlamydomonas reinhardtii* (n=3) and *Chlorella* sp. (n=16)). Unlike fish and invertebrates, copper appears to become more acutely toxic to algae with increasing pH. When all data are considered, *P. subcapitata* is the most sensitive species, with more than 4 studies available for each pH band: the lowest geometric mean E_rC_{50} (duration

not specified) is 104.9 µg/L (n=12) at pH >7.5-8.5 (alkaline). *P. subcapitata* is still the most sensitive species when data are normalised for a DOC level of 2 mg/L, with a lowest geometric mean E_rC_{50} (duration not specified) of 31.6 µg/L (n=11) at pH >7.5-8.5 (alkaline), which is effectively the same result as for *C. reinhardtii* (31.4 µg/L, n=1). For comparison, the E_rC_{50} values at pH 5.5-6.5 (acidic) are above 100 µg/L for all species regardless of DOC normalisation.

RAC notes that no acute data are presented for *Lemna* sp., whereas chronic data are available (this is briefly discussed further below).

Long-term fish toxicity

Chronic data are available for three species (*O. mykiss*, *P. promelas* and Brook Trout *Salvelinus fontinalis*). The DS has separated mortality, growth and reproduction endpoints for each species, giving 70 chronic endpoints in total. However, the number of actual studies is lower since more than one endpoint will have been reported for some studies. RAC notes that the most sensitive endpoint should be selected from a study for a particular species, so RAC is uncertain how much double counting of studies has taken place. The data set includes two specifically commissioned studies for *O. mykiss* and *P. promelas* at acidic pH, and some previously accepted data have been re-evaluated by the DS. Nevertheless, there still remains a relative scarcity of information for the acidic pH band (a single study for *O. mykiss*, three for *P. promelas* and none for *S. fontinalis*). The available information is summarised in the following Table.

Table : Summary of long-term fish NOEC/EC10 data (µg/L) normalised to a DOC level of 2 mg/L

Species	End point	pH band		
		Acidic	Neutral	Alkaline
Oncoryhchus mykiss	Mortality	43.8 (n=1)	16.5 or 17.5 (n=2) [a]	60.6 (n=8)
	Growth	43.3 (n=1)	40.5 (n=4)	31.3 (n=5)
	Reproduction	-	-	-
Pimephales promelas	Mortality	14.6 or 17.9 (n=3) [a]	11.6 or 24.8 (n=3) [a, b]	60.5 (n=5)
	Growth	14.6 or 17.3 (n=3) [a, b]	27 (n=4)	63.8 (n=6)
	Reproduction	-	30.6 or 32.7 (n=2) [a]	57 (n=9)
Salvelinus fontinalis	Mortality	-	28.4 (n=4)	42.3 (n=1)
	Growth	-	28.2 (n=4)	42.3 (n=1)
	Reproduction	-	10.7 (n=3) [b, c]	-

Note: a - Lowest value presented first, followed by geometric mean.

b - All of the data are in the same classification range for each pH band and endpoint *without* DOC normalisation, with the exception of *P. promelas* mortality and growth, for which the minimum value is 5.9 µg/L at the neutral pH band and 8.7 µg/L at the acidic pH band, respectively; and *S. fontinalis* reproduction, for which the minimum value is 6.4 µg/L at the neutral pH band.

c - A geometric mean was not derived by the DS because there are less than four data points across the whole pH range for this endpoint.

In summary, the lowest NOEC/EC_{10} value for fish is 5.9 **µg/L** for *P. promelas* mortality at pH >6.5-7.5 (not normalised for DOC level). If the geomean is used irrespective of the number of available data points, the lowest NOEC/EC_{10} value for fish is 6.4 **µg/L** for *S. fontinalis* reproduction at pH >6.5-7.5 (not normalised for DOC level). If DOC normalisation is taken into account, the lowest NOEC/EC_{10} value for fish is 10.7 **µg/L** for *S. fontinalis* reproduction at pH >6.5-7.5.

RAC notes that the long-term mortality NOEC/EC_{10} for *P. promelas* (not normalised for DOC level) is in the range 10.1-13.8 µg/L at acidic pH, which is effectively the same as the acute LC_{50} value selected for this species (12.1 µg/L). The same conclusion can be drawn when DOC normalisation

is performed (acute LC_{50} of 14.9 µg/L, long-term mortality NOEC/EC_{10} of 14.6 or 17.9 µg/L). Further comments on this are provided in the section on public consultation.

In addition, RAC notes that there is no information about reproduction for any fish species at acidic pH, or any data about the long-term sensitivity of *D. rerio*, which may be highly acutely sensitive at acidic pH (see discussion under acute toxicity above).

Long-term invertebrate toxicity

44 individual chronic data points are available for two "standard" aquatic invertebrate species (*D. magna* and *C. dubia*), but the DS only discusses the data for *D. magna* (for which there are about 25 data points). There are only two data points for the neutral pH band, but more than 4 studies are available for the other two pH bands, with greatest sensitivity apparent at acidic pH. The geometric mean 21-d $NOEC_{reproduction}$ values are 13.2 µg/L (not normalised for DOC) and 10.5 µg/L (normalised for a DOC level of 2 mg/L) at pH 5.5-6.5 (n=7). It should be noted that these are effectively the same as the acute EC_{50} values for mortality, and further comments are provided in the section on public consultation.

In addition, there is only one study reporting effects on growth, in the alkaline pH band (21-d $NOEC_{growth}$ = 12.6 µg/L, regardless of DOC normalisation). RAC notes that if the same trend in toxicity applies as for other endpoints, a lower 21-d $NOEC_{growth}$ (potentially below 10 µg/L) cannot be ruled out for *D. magna* at pH 5.5-6.5.

Long-term algal/macrophyte toxicity

Over 50 individual chronic data points are available for three "standard" algal species (*P. subcapitata* (n=34), *C. reinhardtii* (n=4) and *Chlorella vulgaris* (n=16)) and the macrophyte *Lemna minor* (n=1). Due to the limited number of data points for some species and pH ranges RAC considers that it is not possible to draw a clear conclusion about chronic toxicity trends with pH. When data are not normalised for DOC, *C. reinhardtii* is the most sensitive species, with a lowest NOE_rC (duration not specified) of 22 µg/L at pH 5.5-6.5 (n=2; the geometric mean is 62.6 µg/L). This is similar to the NOE_rC (duration not specified) of 30 µg/L for *L. minor* (n=1) at pH 5.5-6.5. When the data are normalised to a DOC level of 2 mg/L, the lowest geometric mean NOE_rC (duration not specified) is 13.3 µg/L (n=15) for *P. subcapitata* at pH >6.5-7.5.

For comparison, the acute and chronic data for *P. subcapitata* and *C. reinhardtii* are presented in the following Table (with acute-to-chronic ratios (ACRs) calculated by RAC).

Table: Summary of algal toxicity data (µg/L) normalised to a DOC level of 2 mg/L

Species	End point	pH band		
		Acidic	Neutral	Alkaline
Pseudokirchneriella subcapitata	Acute E_rC_{50} [a]	132.6	33	31.6
	Chronic NOE_rC [a]	34.9	13.3	14.1
	ACR	*3.8*	*2.5*	*2.2*
Chlamydomonas reinhardtii	Acute E_rC_{50} [b]	143.2	80.4	31.4
	Chronic NOE_rC [b]	61.7	27.4	24.7
	ACR	*2.3*	*2.9*	*1.3*

Note: a - Geometric mean.

b - Lowest value as there are insufficient data for a geometric mean to be derived in accordance with the CLP Guidance.

RAC notes that if the same ACRs are applied to the *L. minor* NOE_rC (75.8 µg/L when normalised to a DOC level of 2 mg/L), the putative *Lemna* E_rC_{50} would be in the range 136 – 290 µg/L, providing some reassurance that it is unlikely to be an especially acutely sensitive species.

ERV derivation

The lowest acute and chronic toxicity values selected by the DS are summarised in the following Table. This is based on geomeans only if there are four or more data points for a species in a particular pH band (otherwise the lowest value is selected).

Table: ERVs derived by the Dossier Submitter (µg/L)

		pH band		
		5.51-6.5 (acidic)	>6.5-7.5 (neutral)	>7.5-8.5 (alkaline)
Values not normalised for DOC level				
Acute ERV	$L(E)C_{50}$	12.1 (*Pimephales promelas*)	11.7 (*Danio rerio*) [a]	40 (*Ceriodaphnia dubia*)
Chronic ERV	EC_{10} / NOEC	8.7 (*Pimephales promelas*)	5.9 (*Pimephales promelas*)	12.6 (*Daphnia magna*)
Values normalised to a DOC level of 2 mg/L				
Acute ERV	$L(E)C_{50}$	11 (*Daphnia magna*)	24.1 (*Ceriodaphnia dubia*)	31.4 (*Chlamydomonas reinhardtii*)
Chronic ERV	EC_{10} / NOEC	10.5 (*Daphnia magna*)	10.7 (*Salvelinus fontinalis*) [b]	12.6 (*Daphnia magna*)

Note: a - As noted above, RAC does not think this value should be used as it represents very low hardness conditions. The next lowest value is 14 µg/L based on data for *C. dubia*.

b - There is a mistake in Table 92 in the CLH report, where the lowest chronic value with DOC normalisation at the neutral pH band is incorrectly stated to be 5.6 µg/L for *O. mykiss*.

When geomeans are applied, even if there are less than four data points for a species in a particular pH band, effectively the same ERV values are obtained, with the exception of the chronic ERV at acidic pH without DOC normalisation (for which a value of 11.4 µg/L is obtained for *P. promelas*, instead of 8.7 µg/L).

Since similar ERV values are obtained when DOC normalisation is performed, the non-normalised ERVs were carried forward for comparison with the environmental classification criteria.

T/Dp data

Based on the Guidance on the Application of the CLP criteria (2015) the classification of metals is based on a comparison of acute and chronic ERVs (derived from soluble metal species) with the concentration of metal ions in solution after a period of 7 days (short-term test) and 28 days (long-term test), respectively, at different loadings following the T/Dp protocol. Two studies are available for granulated copper. The first (ECTX, 2016a) used one particle of granulated copper in each vessel to attain the desired mass loading of 1 mg/L at pH 6. A copper release of 1.4 µg/L was obtained after 7 days and 6.0 µg/L after 28 days (coefficients of variation were 23 and 27 %). To overcome the high variability, a second study (ECTX, 2016b) was performed with granulated copper particles embedded in epoxy resin. This reportedly allows the exposed surface area to be set more accurately, avoids abrasion and the surfaces were polished before exposure. These results had much lower coefficients of variation (7—11 %) and showed higher copper releases than the first experiment as indicated in the Table below, so the DS prefers the results of this second study for classification purposes.

Table: T/Dp releases from granulated copper at a loading of 1 mg/L

Time	Copper concentration **(µg/L)** [a]		
	pH 6	pH 7	pH 8
7 days	3.4	2.3	1.2
28 days [b]	13	8.6	4.9

Note: a - Considering the specific surface area of granulated copper of 2.56 mm^2/mg.
b - Values were also extrapolated to a loading rate of 0.1 mg/L, yielding copper concentrations of 1.3, 0.86 and 0.49 µg/L at pH 6, 7 and 8, respectively. Extrapolation is in principle allowed according to the CLP Guidance (footnote 106 in Annex IV.2.2.3), but no further details are provided about this extrapolation in the CLH report (but see supplemental analysis below).

A comparison with the ERVs (Table above) demonstrates that dissolution of granulated copper over acute time periods at a loading of 1 mg/L does not lead to concentrations of dissolved metal ions that exceed the acute ERVs, *i.e.* no acute classification is proposed. Dissolution over chronic time periods at a loading of 1 mg/L leads to concentrations of dissolved metal ions that exceed the chronic ERVs at acidic and neutral pH. The extrapolated concentrations for a notional loading rate of 0.1 mg/L are below the chronic ERVs at all pHs. Therefore the DS proposes to classify this substance as Aquatic Chronic 2.

Comments received during public consultation

One Member State Competent Authority (MSCA) made specific comments on the environmental classification (supporting the proposal to classify as Aquatic Chronic 2), with all other comments submitted by Industry and individuals or organisations with connections to them. An additional MSCA made comments about the definition of the substance to be covered by the proposal. The comments cover a range of issues, which can be summarised as follows:

a) *A request to specify the term "granulated" including particle size and specific surface area*: This is provided at the beginning of this opinion.

b) *Further consideration of "rapid removal"*: Additional arguments are available in the copper REACH registration dossier, but have not been submitted separately during public consultation. RAC therefore cannot incorporate them into the current opinion.

c) *Preference to use data for "standard test species"*: RAC believes that, in principle, it is preferable to base classification decisions on data from standard test guideline studies, since these methods have been ring-tested and approved for use for regulatory purposes. However, the data selection in the CLH dossier is not consistent – some "non-standard" fish and algal species were included for some endpoints (*Salvelinus fontinalis* and *Chlamydomonas reinhardtii*), and other standard species that have been used to make classification decisions for other substances (and referred to in ECHA guidance) have been omitted entirely without adequate explanation (*e.g.* crustaceans (including *Ceriodaphnia* sp., *Daphnia pulex*, *Gammarus* sp.), insects and molluscs). RAC considers that these should be included in the data set and subject to grouping and data normalisation for appropriate abiotic conditions (see supplemental analysis below).

d) *Provision of further "chronic" studies for P. promelas which are claimed to support the view that there is no significant trend in toxicity between pH 6 and 7*: This includes a new standard 7-d US EPA "short-term chronic" study at pH 6 available in draft (OSU, 2017). The Industry points out that including these data in the acidic pH band for *P. promelas* increases the number of chronic data points to four and so a geometric mean can be derived (13.3 and 13.9 µg/L for mortality and growth, respectively, without DOC normalisation), replacing the minimum value of 8.7 µg/L for this species and pH band (non-normalised). The non-normalised chronic ERV at pH 5.5-6.5 then becomes 13.2 µg/L (*D. magna* $NOEC_{reproduction}$; geometric mean of 7 values).

RAC notes that 7 days is rather short for a chronic fish endpoint. The acute OECD TG 203 duration is 4 days; the OECD TG 212 (Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages), which is used as a chronic test, specifies 8-9 days for *P. promelas*, and is considered less sensitive than the Early Life Stage test. The main difference between the Norberg & Mount (1985) study and OECD TG 212 seems to be that the larvae were fed from the outset (the OECD test begins with sac-fry feeding on the yolk sac). It is possible that feeding might reduce bioavailability of the copper due to the addition of organic carbon in the water. On the other hand, in this case, the 7-d growth results of Norberg & Mount (1985) were very similar to those derived from separate 32-d Early Life Stage and 327-d full life cycle tests (reported in 1978 and 1969, respectively). RAC has not attempted to assess whether this relationship holds if a larger data set including more modern studies were examined.

RAC also notes that using this information creates some inconsistency with the acute data set. For example, when the new data are taken into account the "chronic" mortality LC_{10} for *P. promelas* (not normalised for DOC level) is around 13 µg/L at acidic pH, which is slightly higher than the acute LC_{50} value selected for this species (12.1 µg/L). The same conclusion can be drawn when DOC normalisation is performed, and is also apparent for the invertebrate *Daphnia magna*. This might simply reflect the differences in the amount of data available (and also potentially hardness), but raises some doubts over the comparability of the acute and chronic data set. This is discussed further in the section that presents RAC's assessment of the classification below. In addition, RAC notes that there is no information about reproduction for any fish species at acidic pH, or any data about the long-term sensitivity of *Danio rerio*, which may be highly acutely sensitive at acidic pH (see discussion under *Acute Fish Toxicity* above).

The implications of excluding the 7-d data are provided in the supplemental analysis below. On balance, RAC prefers not to include them.

e) *Appropriateness of data aggregation and summarisation for data-rich substances*: In principle, RAC considers that splitting the data to reflect the pH bands defined for T/Dp testing is appropriate. In addition, it seems logical to attempt to minimise variability in the data set based on known factors such as the influence of hardness and DOC. However, in this context, RAC notes that the justification to normalise the data to a DOC level of 2 mg/L, is weak and not necessarily appropriate (as it is a maximum recommended in the OECD TGs, which is likely to protect against the toxic effect to some extent). It also introduces some uncertainties due to the omission of studies that lack sufficient background information (which also reduces the size of the data set). In addition, this may not be entirely consistent with the T/Dp data, which are produced in the absence of DOC. Therefore RAC is not in a position to recommend an appropriate DOC value. Both normalised and non-normalised ERVs are presented in the RAC assessment below, and the most stringent classification derived. RAC notes that a BLM approach might have been attempted, although this is based on an assumption that relationships established for a small number of species are generally applicable to others. RAC also considers that the resulting limitations in the data set must be recognised even if the overall number of data points is very large. An example is the lack of acute toxicity data for Zebrafish at acidic pHs, which might prove sensitive (see discussion under *Acute Fish Toxicity* above).

In terms of choice of values, RAC recognises that there needs to be a way of avoiding the default selection of a very low value from a large data set due to the method of splitting the information, provided that factors that can affect the variability in toxicity are fully considered. In particular, sensitive conditions should not be overlooked or 'diluted' by the

choice of averaging method. Consequently, RAC considers that it is only appropriate to use the geometric mean when there are 4 or more data available in a pH band for specific endpoints (*e.g.* reproduction) for a species. Preferably the same effect concentrations should be used, but if insufficient data points are available EC_{10} and NOEC values can be mixed.

RAC agrees that it would be worthwhile to perform a "reality check" of the relationship between pH and selected ERV values based on specific experimental studies that have investigated effects of pH on copper toxicity, notably for fish (*e.g.* Erickson et al., 1996; Ng et al., 2010; and OSU, 2016), provided that these followed typical standard approaches to measuring acute/chronic toxicity. For example, the OSU (2016) study included a 56-days Early Life Stage test with juvenile *O. mykiss* performed under similar conditions to the study of Ng *et al*. (2010), but involving formal replication, statistical assessment, acclimation of organisms to low pH, and pre-equilibrated test waters. The EC_{10} values were 28.5 (survival) and 36.0 (wet weight) µg/L at pH 6, and 49.3 (survival) and 47.3 (wet weight) µg/L at pH 7. The Industry concludes that there are little or no sensitivity differences to fish between pH 6 and 7 based on this information. RAC notes that the fish appear to have been slightly more sensitive under acidic conditions, although without information on the uncertainty in the EC_{10} values, these data neither confirm nor exclude a pH effect.

Further evidence from Species Sensitivity Distribution (SSD), bootstrapping and Biotic Ligand Model (BLM) approaches would also be useful to consider in terms of the overall weight of evidence. However, this has not been performed by the DS or provided during public consultation, and is not essential for a conclusion. Further interpretation of such approaches would in any case also benefit from a discussion at global level.

f) *A suggestion that the lowest chronic NOEC/EC_{10} value for P. promelas mortality at neutral pH without DOC normalisation (5.9 µg/L) is an outlier*: RAC tends to agree that this value may be unusually low (see RCOM for further discussion) but notes that when DOC normalisation is applied, the value changes to 11.6 µg/L, which is preferred as a more relevant indicator of toxicity.

g) *A suggestion to use the results of an old (1974) study on reproduction in S. fontinalis which showed no effects up to the highest test concentration of 9.4 µg/L as supporting information to justify the use of a geometric mean at neutral pH for this species and endpoint*: There is (undescribed) "uncertainty" related to the pH during this test and given the age of the test RAC does not think sufficient justification has been provided to include this data point.

h) Industry agrees with the way that the transformation/dissolution protocol data have been used, and highlights that the classification proposal is specific for the test material used. RAC has added a note to the opinion about this.

i) Based on Industry's re-analysis of the data set, they propose not to classify granulated copper as hazardous to the aquatic environment. This depends on the selection of geometric mean or the lowest value, data normalisation and also the inclusion of chronic data for relevant additional species, as well as the way inconsistencies between the acute and chronic data sets are handled.

j) It should be clarified that the proposal does not cover nanoforms of copper. RAC agrees and has added a note to this effect.

Assessment and comparison with the classification criteria

Degradation

Based on the data provided in the CLH dossier and submitted during public consultation, granulated copper is not considered to be rapidly transformed by normal environmental processes. RAC recommends that future CLH dossiers for other copper compounds could take account of all relevant information once an internationally agreed approach to this issue has been reached. This may in turn affect classification decisions drawn for this substance and previous copper compound cases.

Bioaccumulation

The bioaccumulation behaviour of copper (II) ions is complicated by essentiality and homeostatic mechanisms in organisms, but does not need to be considered further because it does not influence the determination of the chronic M-factor (in view of the conclusion about removal).

Aquatic toxicity

RAC has not independently verified all of the ecotoxicity information in the CLH dossier given the quantity of data and previous evaluations. Based on the information provided in the CLH report, public comments and supplemented by the DS during RAC discussions (see supplemental analysis), RAC considers that the following ERVs are most appropriate:

		pH band		
		5.51-6.5 (acidic)	>6.5-7.5 (neutral)	>7.5-8.5 (alkaline)
Values not normalised for DOC level				
Acute ERV	$L(E)C_{50}$	12.1 (*Pimephales promelas*)	11.7 (*Danio rerio*)	40 (*Ceriodaphnia dubia*)
Chronic ERV	EC_{10}/NOEC	13.2 (*Daphnia magna*) [a]	4 (*Ceriodaphnia dubia*) [b]	12.6 (*Daphnia magna*)
Values normalised to a DOC level of 2 mg/L				
Acute ERV	$L(E)C_{50}$	11 (*Daphnia magna*)	24.1 (*Ceriodaphnia dubia*)	31.4 (*Chlamydomonas reinhardtii*)
Chronic ERV	EC_{10}/NOEC	10.5 (*Daphnia magna*)	6.2 (*Ceriodaphnia dubia*) [b]	11.8 (*Ceriodaphnia dubia*)

Note: a – If 7-d data for *P. promelas* were used, the ERV would be 8.7 µg/L (n=3), or 13.3 µg/L if the OSU (2017) study is taken into account.

b – This is the main difference from the DS's proposal. The lowest reported long-term NOEC at neutral pH for *C. dubia* in the previous CLH reports for the copper compounds was 7.4 µg/L, which was a geomean of the 4 available (non-normalised) NOEC values without distinguishing between mortality and reproductive effects. As the CLH dossier now splits this information, the lowest NOEC becomes 4 µg/L without DOC normalisation, corresponding to 6.2 µg/L with DOC normalisation.

The data aggregation exercise results in an unusual conclusion for acidic pH, *i.e.* the concentration that causes 50 % mortality in acute tests is effectively the same as that which causes no adverse effects in long-term tests (with the same species in the case of the DOC-normalised values). In a reply to a question from the RAC rapporteur, the DS considers that the acute-to-chronic ratios (ACRs) are generally low, and tend to decrease with decreasing pH (approaching unity at around pH 6). RAC has some concerns about this general conclusion, because although there may be reasons for similar acute and chronic sensitivities (*e.g.* acclimation, provision of food that could affect bioavailability, etc.), there is far more acute than chronic data especially at lower pH, which might produce misleading ACRs (since the result is highly dependent on the representive nature of a very small number of chronic values). As an

example, an ACR below 1 is obtained for *O. mykiss* mortality at acidic pH, implying that the organisms are less sensitive over long-term exposure and/or at sensitive life stages. As a possible "worst case", applying the apparent ACR for *C. dubia* from the DOC-normalised ERVs at neutral pH (3.9) to the acute ERV for *D. magna* at acidic pH would result in a theoretical DOC-normalised chronic ERV for *D. magna* of 2.8 µg/L at acidic pH.

The change in species sensitivity across the pH bands could also be an artefact of the varying amounts of data available. RAC concludes that the amalgamation of such a diverse data set is not ideal for classification purposes, and that it might have been better to focus more on standard studies that have been specifically designed to investigate pH variation under specific DOC and hardness conditions in a single laboratory. In the absence of such an analysis, the derived ERVs have to be used.

As pointed out in the discussion above, even though the data set is relatively large, there are still potential information gaps, including for Zebrafish *D. rerio* and Brook Trout *S. fontinalis* at acidic pH (e.g. an acute LC_{50} below 10 µg/L (normalised for DOC) cannot be ruled out). RAC considers that if such data became available, the acute and chronic ERVs at acidic pH could be lower than 10 µg/L.

Before presenting the classifications, it is appropriate to recall the T/Dp data at a loading of 1 mg/L:

Time	Copper concentration **(µg/L)**		
	pH 6	pH 7	pH 8
7 days	3.4	2.3	1.2
28 days	13	8.6	4.9

Acute aquatic hazard

Dissolved copper concentrations arising from granulated copper do not exceed 3.4 µg/L at any pH over 7 days at a loading rate of 1 mg/L. This is below the acute ERVs (⩾ 11-12 µg /L) by at least a factor of three, so the substance will not achieve acutely toxic dissolved concentrations over a relevant time period at 1 mg/L. No classification Acute Aquatic toxicity is warranted.

Chronic aquatic hazard

Dissolved copper concentrations arising from granulated copper are 13 and 8.6 µg/L over 28 days at a loading rate of 1 mg/L at acidic and neutral pH, respectively. These exceed the chronic ERVs for these pH bands (13.2 or 10.5 and 4 or 6.2 µg/L, respectively). The extrapolated copper concentrations at a notional loading rate of 0.1 mg/L (i.e. 0.49 – 1.3 µg/L) do not exceed the chronic ERVs at any pH. Chronic toxicity may therefore be expressed at a loading rate of >0.1 to ≤1 mg/L, which results in classification as Aquatic Chronic 2 for a substance that is not rapidly transformed. This conclusion only applies to the substance that was tested in the T/Dp test, since the metal release per unit surface is an intrinsic property of the material.The chronic ERV would have to be less than 1.3 µg/L at acidic pH to affect this conclusion, which seems unlikely even though there is some uncertainty in the data set.

Conclusion on the classification

RAC agrees with the DS that granulated copper requires classification as Aquatic Chronic 2; H411 –Chronic to aquatic life with long lasting effects.

This opinion does not address either copper massive or powder (the CAS and EC number given in the proposal is in fact for metallic copper, and so to avoid misunderstandings a clear message may need to be provided if a future entry for granulated copper). Nano-forms should also be considered separately.

The ERVs selected for this substance may also affect the classification of other copper compounds already considered by RAC, but this has not been assessed.

Additional references

Rodriguez, P.H., Adams, W. and Delbeke, K., 2007. Methodology for aquatic hazard classification of massive metal forms: the copper case. Proceeding of the sixth International Copper Conference, Copper 2007, Volume VI pp 217-228. Available from the VRAR, 2008, annex K2, slightly amended afterwards.

Skeaff, J.M. and D.J. Hardy, 2005. Bioavailability Test Studies of Copper and Iron Powder and of Sintered Alloys at pH 6. CANMET-MMSL 04-041(CR)/Contract No. 602785. Available from the Copper Voluntary Risk Assessment, 2008, annex K4.

ANNEXES:

Annex 1 The 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 RAC (excluding confidential information).