European Copper Institute
Copper Alliance

ECI COMMENTS TO

CLH REPORT: PROPOSAL FOR HARMONIZED CLASSIFICATION AND LABELLING OF COPPER OXIDE (CUO)

These comments also reflect the considerations of the following task forces and consortium;

European Antifouling Copper Task Force

Wood Preservative Copper Task Force

The European Union Copper Task Force (Plant Protection Products Regulation [PPPR])

Copper Compound Consortium

ABSTRACT

We acknowledge and appreciate the alignment with the copper risk assessment dossier as well as the incorporation of some post risk assessment data.

For most endpoints, the data used and interpretation of the data reflect the hazard profiles agreed in the copper risk assessment report (RAR) and used for the CuO REACH dossier.

For some endpoints, we noted some differences in data-interpretation between the copper oxide CLH report and REACH dossier. We have therefore focussed the review on these endpoints and propose to revise the classification to:

No classification warranted for acute inhalation[1]

Environmental hazard Acute category 1. M factor = 1[2].

Environmental hazard Chronic category 2[3].

[1] CLH report proposal: Acute Tox 2 – H330
[2] CLH report proposal: Acute 1, M factor 10
[3] CLH report proposal: Chronic 1, M Factor 1

1) INTRODUCTION

We appreciate the opportunity to review the CLH report but do regret the significant overlap between the public consultation period and the year-end holidays.

We acknowledge and appreciate the alignment between the CLH report and the copper RAR as well as the incorporation of some post risk assessment data. For most endpoints, the data used and interpretation of the data reflect the hazard profiles agreed in the copper risk assessment and used for the copper oxide REACH dossier.

Please find below a more detailed review for hazard endpoints, demonstrating differences in classification between the CuO CLH report and REACH dossier.

2) HUMAN HEALTH HAZARDS

Acute Inhalation Classification Proposal

In 2008 the RAR concluded that there was no need to classify copper oxide by the inhalation route (Human Health, Appendix 7). An alternative proposal is now presented in the CLH document. This is based on read-across from copper dihydroxide data and relies on the hypothesis that since these two compounds have similar water solubility values, the inhalation effects will also be comparable. Therefore, it has been proposed to classify copper oxide as H330, fatal if inhaled.

However, when the available acute toxicity and irritation classifications are compared between copper oxide and copper dihydroxide, it can be clearly seen that copper dihydroxide is a much more toxicologically significant compound than copper oxide. This is probably due to the alkaline nature of copper dihydroxide and the particle shape of this particular copper compound. The following table shows the proposed CLH classifications of copper oxide and copper dihydroxide.

Classification	Copper oxide	Copper dihydroxide
Oral	No classification	Acute Tox 4 (H302)
Inhalation	Fatal if inhaled (H330)*	Fatal if inhaled (H330)
Eye irritation	No classification	Risk of serious eye damage (H330)

*Based on read across

Due to the differences observed in acute toxicity studies, it does not appear to be justified to read-across from copper dihydroxide to copper oxide for the purposes of acute inhalation classification.

The effects observed in the inhalation study with copper hydroxide are probably influenced by pH and the effect of the needle particle shape on lung tissue and this effect would not be expected to occur with spherical particle like copper oxide.

Whereas the bioavailability of copper dihydroxide has been shown to be similar in relation to other copper compounds used in plant protection products, including dicopper oxide (Cu_2O) (Himmelstein, 2003), copper oxide has been shown to have a low bioavailability potential in comparison to other copper compounds in animal studies. These data are taken from the

copper oxide REACH dossier and show that copper oxide is the least bioavailable compound from those tested.

For the oral exposure route, in a series of bioavailability studies, conducted by several authors the bioavailability of copper sulfate was compared to other less soluble copper compounds including copper oxide, dicopper oxide and copper carbonate. .

In all cases, copper sulfate was shown to be more or equally bioavailable in relation to the other four copper salts (Table 1). Although the species tested are not usual species used in regulatory guidelines, the results are consistent when evaluating a number of studies and appear to be reproducible. In addition, the studies have measured copper levels in the most important organ and body fluid in determining copper adsorption from the gastro-intestinal tract, namely the liver and bile.

Table 1: Relative bioavailability of supplemental copper sources

Source of copper	Species			References (and applicable species)
	Poultry	Swine	Cattle	
Copper sulfate	100	100	100	Aoyagi and Baker, 1993 (poultry) Baker *et al.,* 1991 (poultry) Buescher *et al.,* 1961 (swine) Cromwell *et al.,* 1989 (swine) Kegley and Spears, 1994 (cattle)
Copper oxide	0 (3)	30 (4)	15 (2)	
Cuprous oxide	95.2(2)	-	-	Aoyagi and Baker, 1993 (poultry) Baker *et al.,* 1991 (poultry)
Basic copper carbonate	115 (1)	60 (1)	-	Allen *et al.,* 1961 (swine) Aoyagi and Baker, 1993 (poultry)
Copper carbonate	-	95 (1)	-	Buescher *et al.,* 1961 (swine)

Average numbers are rounded to the nearest '5' and expressed relative to response obtained with copper sulfate. Number of studies or samples involved indicated within parenthesis.

The low bioavailability of copper in copper oxide, relative to that of copper in the sulfate salt, was also demonstrated in the rat following administration at adequate dietary levels (Rojas *et al.,* 1996).

The low bioavailability can also be observed in lung fluid bioelution data (see Table 2).

Data on the solubility of cupric oxide (CuO), cuprous oxide (Cu_2O) and cuprous thiocyanate (CuSCN) in lung fluids are taken from a bioelution study that is summarised as supporting information in the copper oxide REACH dossier (Rodriguez, 2009). Of two available studies, this one is considered most appropriate as the solubility level tested (100 mg/l) was equivalent to the doses used in the available animal studies.

Table 2: Comparison of Copper Compound Solubility in Water and Artificial Lung Fluid (ALF) with Acute Inhalation Classification Status.

Compound	Solubility in Water (mg/L)	Solubility in AAF** (Mean as Cu, mg/L)	Solubility in AIF** (Mean as Cu, mg/L)	Acute Inhalation Classification based on animal data
CuO	0.394 (pH 6.0)	3.44 – 7.32 (pH7.4)	3.09 – 7.86 (pH 7.4)	--
Cu_2O	0.639 (pH 6.5 – 6.6)	15.13 – 22.97 (pH 7.4)	17.93 – 21.50 (pH 7.4)	H302: Harmful*
CuSCN	1.91 – 2.03 (pH 7.0)	8.80 (pH 7.4)	6.20 (pH 7.4)	Not Classified

*Proposed classification based on available data.
**AIF = Artificial Interstitial Fluid; AAF = Artificial Alveolar Fluid.

For further information on the acute inhalation studies on Cu2O and CuSCN, please refer to the CLH documents on these compounds.

As shown in Table 2 the most soluble of the compounds considered in both water and ALF is cuprous oxide. This compound is classified as harmful by inhalation on the basis of a classic acute inhalation test in rats.

The other compound for which animal data are available is cuprous thiocyanate. While this is marginally more soluble in water than cuprous oxide, its solubility in ALF (and indicative of lower bioavailability) is significantly lower. This is reflected in the fact that cuprous thiocyanate is not classified on the basis of its acute inhalation toxicity in an equivalent acute inhalation study in the rat.

Copper oxide is less soluble in water than cuprous thiocyanate and cuprous oxide and is also significantly less soluble in ALF, and this is indicative of low bioavailability (also substantiated by the results of acute oral and dermal toxicity studies with cupric oxide).

When **all** of the available data on copper oxide are evaluated in a weight of evidence approach;

- Differences in pH,
- Differences in particle shape
- Differences in known toxicological profiles
- Differences in bioavailability when comparing animal data and in vitro bioelution data,

It can be concluded that the reference substance, copper dihydroxide, is not comparable to the target substance, copper oxide. Therefore it is proposed that the classification proposal in the RAR for copper oxide by the inhalation route be retained for this harmonised classification. Classification is not warranted by the inhalation route for copper oxide.

3) ENVIRONMENTAL HAZARDS

In the REACH dossier, we derived the following classification for environmental hazard:

Acute category 1. M factor = 1.
Chronic category 2.

The difference in classification is related to the assessment of the solubility of copper oxide (see section 3.1 below).

We also noted some differences in data-interpretation and data-aggregation between the CLH report and REACH report, without influence to the classification outcome (see section 3.2 below).

3.1 TRANSFORMATION/DISSOLUTION DATA

The CLH report used the solubility data from the RAR to conclude that CuO is fully soluble[4]. However, OECD protocols on water solubility are not applicable to metals and sparingly soluble metal compounds, which are characterized by transformation mediated solubilisation.

Rodriguez et al., 2000[5] performed transformation dissolution tests on CuO (also included in REACH 2013 update dossier). The resulting dissolved copper concentrations after 24 hours transformation dissolution demonstrated low solubility (<1%) with no exceedence of the ERV at 1 mg/L across the pH range (pH 6 to 8). These results suggest that CuO could be considered poorly soluble and data from the full transformation/dissolution test (Table 3) have been used to derive the environmental hazard classes for CuO. We therefore propose to consider transformation/dissolution in the classification of CuO.

Table 3: Transformation/dissolution of copper oxide at 1 mg/L loading, expressed as mg dissolved Cu/L

Transformation/dissolution				
Loading [mg CuO/l]	Time [days]	mg dissolved Cu/L		
		At pH 6	At pH 7	At pH 8
1	7	0.049	0.005	0.000
1	28	0.210	0.009	0.001

3.2 ECOTOXICITY DATA

The RAR ERVs, retained in the CLH report, are slightly higher than the ones defined in the REACH dossier because in the RAR geometric mean values were derived, even when only 2 and 3 data-points per species were available. However, in the REACH report, the geometric mean was only applied if 4 or more data-points were available, which slightly lowered some species-specific reference values (see Van Sprang and Delbeke, 2010 - Attachment 1). Table 4 summarises the ERVs retained from the DAR, RAR and REACH, expressed as dissolved copper-ions.

[4] Please note that the solubility reported in the RAR at pH 9 was not 0.01 mg/L but ≤0.01 mg/L
[5] Report available from the copper RAR (2008) (Annex K3)

Table 4: Summary of the acute and chronic ERVs for copper, expressed as mg dissolved Cu/L

Source	pH range	Acute ERV Cu	Chronic ERV Cu
RAR	5.5-6.5	0.029	0.020
	>6.5-7.5	0.047	0.007
	>7.5-8.5	0.030	0.016
REACH	5.5-6.5	0.025	0.020
	>6.5-7.5	0.035	0.007
	>7.5-8.5	0.030	0.011
	across all pHs	0.034	0.015

Note: In the RAR and the REACH dossier, the ecotoxicity data from *P. promelas* at pH 6 (Erickson *et al.,* 1996) were rejected and it may be clarifying to also mention this in the CLH report.

> The test was performed with larvae (< 24 h old) in a flow-through with a very short retention time (± 45 min.), using a diluted reconstituted medium (prepared from Lake Superior water through reverse osmosis) with a low hardness (22 mg/l CaCO3) and DOC concentration (reverse osmosis). This test performed represent worst case conditions explaining therefore this low LC50 value. Moreover the observed pH dependency observed for *P. promelas* at (sensitivity at pH 6 versus pH 7) is unexpected and may be related to insufficient adaptation to low pH conditions (from Van Sprang and Delbeke, 2010 -Attachment 1).

This difference does not influence the classification outcome.

3.3 PROPOSED ENVIRONMENTAL CLASSIFICATION

Based on the comparison between the pH specific 7 days and 28 days transformation/ dissolution data and the pH specific acute and chronic ERVs (see Table 5), the following is concluded:

At pHs 6, 7 and 8, at a loading of 1 mg/L, the dissolved copper concentration after 7 days transformation/dissolution were measured. The dissolved copper concentration after 7 days transformation/dissolution at lower loadings (0.1 and 0.01 mg/l) were calculated from linear extrapolation of the 1 mg/L transformation/dissolution data (Table 5, see also Figure 1). Comparison between the acute ERVs and the 7 day dissolved copper concentrations (Table 5) shows copper concentrations exceed the ERV at the 1 mg/L (tested) but not at 0.1 mg/L (extrapolated). These data therefore allow for an aquatic **Acute 1 - H400, M factor = 1**[6].

[6] CLH report: Acute 1, M factor = 10

Table 5: Transformation/dissolution of CuO (measured at 1 mg/L and extrapolated to lower loadings) and ecotoxicity reference values, expressed as mg dissolved Cu/L

Transformation/dissolution				
Loading [mg CuO/l]	**Time [days]**	**mg dissolved Cu/l**		
		At pH 6	**At pH 7**	**At pH 8**
1 **0.1 (extrapolated)**	7	0.049 0.005	0.005 <0.001	0.000 <0.001
1 **0.1 (extrapolated)** **0.01 (extrapolated)**	28	0.210 0.021 0.002	0.009 <0.001 <0.001	0.001 <0.001 <0.001
Additional data: Ecotoxicity Reference Values - mg dissolved Cu/ l				
Acute ERV	LC_{50}	0.029 (0.025)	0.047 (0.035)	0.0298
Chronic ERV	NOEC	0.020	0.0074	0.016 (0.0114)

Environmental Reference Values for acute and chronic ecotoxicity, from the CLH report and between brackets from the REACH CSR.

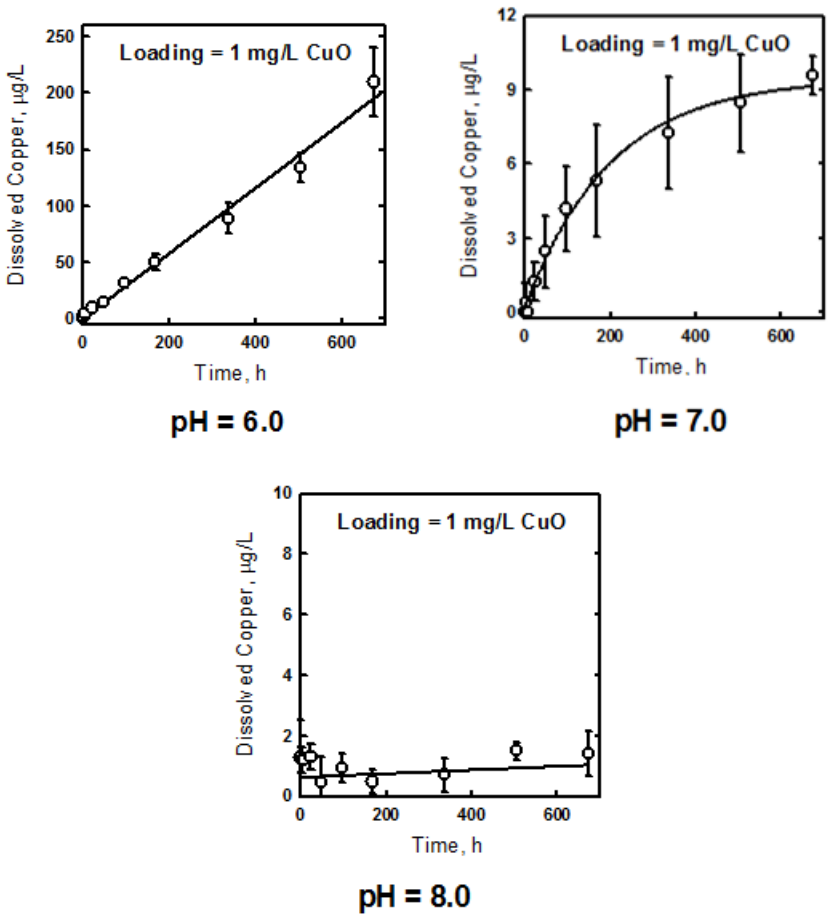

Figure 1: Copper release time course at pH 6.0, 7.0 and 8.0 at 1 mg/L loading. The 95% of confidence curve fit functions are shown.

For the assessment of chronic classification, the 28 day transformation/dissolution dissolved copper concentrations at pHs 6, 7 and 8, and a loading of 1 mg/L were measured. Dissolved copper concentrations after 28 days transformation/dissolution have been predicted for lower loadings (0.1 and 0.01 mg/L) by linear extrapolation from the data at 1 mg/L (Table 5). Comparison between the chronic ERVs and these dissolved copper concentrations (Table 5) shows that at pH 6 the dissolved copper concentrations were higher than the ERV at 0.1 mg/L, but not at 0.01 mg/L. At pH 7 the ERV is triggered at loadings between 1 mg/L and 0.1 mg/L. At pH 8, the dissolved copper concentration at 1 mg/L does not exceed the ERV.

Taking account of the evidence for rapid removal of copper from the water column, the most stringent classification is taken from dissolution data at pH 6. At pH 6, the dissolved copper concentration triggers the lowest ERV (0.020 mg/L) at loadings between 0.01 and 0.1 mg/L. These data and assumptions lead to the environmental hazard **Chronic 2 - H411.**

For comparison purposes, the classification versus solubility for copper compounds and copper flake is presented in Attachment 2 for completeness.

4) RELEVANT ATTACHMENTS

Attachment 1: Van Sprang and Delbeke, 2010

Attachment 2: Classification versus solubility of copper compounds and copper flake

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