European Copper Institute
Copper Alliance

ECI COMMENTS TO

CLH REPORT: PROPOSAL FOR HARMONIZED CLASSIFICATION AND LABELLING OF COPPER OXYCHLORIDE

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 REACH dossiers.

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

Acute Tox. 4 - H302: Harmful if swallowed[1]

[1] CLH Report: Acute Tox. 3 - H301

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 risk assessment dossier as well as the incorporation of some post risk assessment data.

For the environmental endpoints, we noted some differences between the copper oxychloride CLH report and the REACH dossier. These differences did not lead to a different classification. Please find below a more detailed review on the environmental hazard assessment.

2) HUMAN HEALTH HAZARDS

2.1 MOUSE LD50 STUDY

The CLP guidance document section 3.1.2.3.2 Evaluation of non-human data p 263 states that the preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat.

The CLP guidance document section 3.1.2.3.2 Evaluation of non-human data p 263 in case of multiple LD50/LC50s from several species states "In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. However, expert judgement may allow another ATE value to be used in preference, provided this can be supported by a robust justification. If there is information available to inform on species relevance, then the studies conducted in the species most relevant for humans should normally be given precedence over the studies in other species."

Although a study is available for acute oral toxicity in the mouse with lower LD50 values (Haynes, G., 1998), the mouse is not the most appropriate species for the estimation of the acute toxicity of copper oxychloride in the human. The species most relevant for classification is the rat, the preferred species for classification purposes.

The human system is more similar to the rat in relation to copper absorption, distribution in tissues, and ceruloplasmin activity as compared to the mouse (Linder, 1991; Biochemistry of Copper, Plenum Press New York) as shown in Table 1 below.

Table 1: Summary of copper absorption, distribution in tissues, and ceruloplasmin activity across species

Tissue/Organ	Copper concentrations (ppm)		
	Human	Rat	Mouse
Blood Plasma	1.13	1.28	0.38
Liver	6.2	4.6	4.4
Kidney	12	7.9	4.4
Brain	5.2	3.1	4.4
Heart	4.8	5.5	4.0
Spleen	1.5	2.3	-
Lung	1.3	1.8	2.7
Muscle	0.9	1.0	3.9
Skin	0.8	1.7	-
Adipose	0.25	0.35	-
Ceruloplasmin			
half-life (days)	4.5	5.75	-
Oxidase activity (% of human value)	100%	85%	60%

2.1.1 Absorption

In mammals, orally administered copper is absorbed in the stomach and small intestine. The site of maximal absorption appears to differ according to species, with absorption from the stomach and duodenum in rats and absorption from the lower small intestine in hamsters (van Campen and Mitchell 1965; Crampton et al., 1965).

In man, the absorption of copper appears to occur primarily in the stomach and duodenum where acidic conditions favour solubility. This is evident from the study of Earl et al (1954) who showed that following the oral administration of radiolabelled cupric chloride (1.5 to 12.5 mg copper), the isotope appears rapidly in the blood reaching maximum levels within 1 to 3 hour.

Absorption in both rats and humans varies according to diet: for humans on a copper-adequate diet, absorption is 36%; on a low copper diet 56%, and on a high copper diet 12% (Turnlund et al., 1989). Similar figures have been obtained for rats (30-50%).

Data from both rats and humans indicate that in the range of normal intakes, there is some adaptation of absorption relative to need (copper homeostasis): higher percentages of the available copper are absorbed at lower intakes and vice versa.

It appears that rats and mice are quite different in their responses to copper concentrations, the mouse appears more sensitive at lower concentrations, however a tolerance for copper is apparent following longer dosing periods with the compound as compared with the rat (Hébert et al., 1993).

2.1.2 Distribution

Ceruloplasmin is the main source of copper for other tissues. Ceruloplasmin copper is not part of the exchangeable plasma copper pool, and ceruloplasmin does not directly bind or incorporate the metal when exposed to copper ions. Copper is added during the synthesis of ceruloplasmin by the liver. Only when ceruloplasmin bearing newly absorbed copper, is secreted into the plasma does one begin to find appreciable uptake of copper by other tissues. Thus there appears to be two phases of distribution after copper enters the blood: entry into the liver (and kidney), and entry into other tissues. The first may be mediated primarily by

transcuprein, the second by ceruloplasmin (Linder and Hazegh-Azam, 1996). Therefore it can clearly be seen that the rat closely resembles the human in distribution of copper to other tissues due to ceruloplasmin activity.

2.2 CLASSIFICATION

In conclusion the results for the acute oral toxicity test in rats will more accurately predict the effects in humans, and it is strongly recommended to utilise this information for the classification of copper oxychloride. Furthermore in accordance with the CLP Guidance document, acute studies conducted on the rat are preferred to studies conducted on other species.

The classification assigned to dicopper chloride trihydroxide on the basis of acute oral toxicity is **Acute Tox. 4 - H302: Harmful if swallowed**.

References

Crampton, R.F. et al (1965) Observations on the mechanism of absorption of copper by the small intestine. J Physiol 1965 May; 178: 111-26

Earl. C.J. et al., (1954) Metabolism of copper in Wilson's disease and in normal subjects: Studies with Cu-64. The American Journal of Medicine. Volume 17, Issue 2, August 1954, pg 205-213.

Hébert et al., (1993). Subchronic toxicity of cupric sulfate administered in drinking water and feed to rats and mice. National Institute of Environmental Health Sciences, North Carolina and Biotechnical Services Inc, Arkansas. Fund and App Tox, 21: 461-475.

Linder (1991), Biochemistry of Copper, Plenum Press New York

Linder, M.C., and Hazegh-Azam, M. (1996). Copper Biochemistry and molecular Biology. Am J Clin Nutr 1996; 63:797S-811S

Turnlund et al., (1989). Copper absorption and retention in young men at three levels of dietary copper by use of the stable isotope 65Cu1-4. Am J Clin Nutr 1989; 49:870-8

van Campen, D.R. and Mitchell E.A (1965). Absorption of Cu64, Zn65, Mo99, and Fe59 from ligated segments of the rat gastrointestinal tract. J Nutr, 86: 120-124

3) ENVIRONMENTAL HAZARDS

In the CLH and REACH dossier, the following classifications for environmental hazard were derived:

Acute category 1. M factor =10.
Chronic category 2.

Some differences in the assessment were noted as described below.

3.1 ECOTOXICITY DATABASE

In the CLH report, two data-sets are used independently for the classification: the ecotoxicity data from the RAR, based on tests with soluble copper compounds, and the ecotoxicity data from the DAR, based on tests with copper oxychloride.

Only test results expressed as measured dissolved copper concentrations were retained for the CLH report (RAR and DAR data-set) and REACH dossier (RAR data-set). Considering that the ecotoxicity data from the RAR relies on tests with soluble copper compounds while the ecotoxicity data from the DAR relies also on sparingly soluble copper species (Copper oxychloride solubility 1.19 mg/L at pH 6.5 and 0.525 mg/l at pH 10), a comparison between total and dissolved concentrations is therefore relevant to the data-interpretation

- In the RAR total and dissolved concentrations were compared for the chronic toxicity tests, carried out with soluble copper species. The data showed dissolved fractions >72-100% of the total fraction and assessment concluded that almost all copper was present in the dissolved form in the toxicity tests (more details - see RAR, aquatic effects -*Extract section 3.2.2.27).*

- When evaluating the ecotoxicity data from the RAR (Table in section 5.5), up to 40 times lower L(E) C50 values expressed as total versus dissolved copper concentrations were recorded. This indicates that some of the less soluble copper compounds (eg copper oxychloride) may have precipitated and reproducibility and dose–response relationship for dissolved copper concentrations therefore needs further elaboration.

- As proposed in the CLP guidance, ecotoxicity data from tests carried out with fully soluble compounds (cf. RAR/REACH data-sets) are therefore preferred.

- 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, also when only 2 and 3 data-points per species were available. In the REACH report, the geometric mean was only applied if 4 or more data-points are available. This refinement slightly lowered some species-specific reference values (more information from Van Sprang and Delbeke, 2010 – Attachment 1).

Table 2 summarises the ERVs retained from the DAR, RAR and REACH, expressed as mg copper oxychloride/L(after molecular weight translation).

Table 2: Summary of the acute and chronic ERVs for copper oxychloride

Source	pH range	Acute ERV CuOCl	Chronic ERV CuOCl
DAR		0.087	
RAR	5.5-6.5	0.049	0.034
	>6.5-7.5	0.079	0.012
	>7.5-8.5	0.050	0.027
REACH	5.5-6.5	0.042	0.034
	>6.5-7.5	0.059	0.012
	>7.5-8.5	0.050	0.019
	across all pHs	0.058	0.025

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).

3.2 CLASSIFICATION

The CLH and REACH dossiers consider copper oxychloride as fully soluble (1.19 mg/L at pH 6.5 and 0.525 mg/l at pH 10). No transformation dissolution data are available. However, for comparison purposes, the classification versus solubility for copper compounds and copper flake is presented in Attachment 2 for completeness.

The CLH and REACH dossiers consider copper oxychloride as rapid degradable (with evidence for rapid removal of copper from the water column presented).

Classification in both dossiers (CLH and REACH) is therefore based on straight comparison between ERV values (Table 1) and classification cut-off values.

- Table 1 consistently indicated Acute ERV values between <0.1 mg/L and >0.01 mg/L. The assessment therefore confirms the environmental hazard **Acute 1 - H400. M factor = 10.**

- For chronic toxicity, the ERVs are <0.1 mg/L and >0.01 mg/L, confirming the environmental hazard classification entry as **Chronic 2 - H411.**

4) RELEVANT ATTACHMENTS

Attachment 1: Van Sprang and Delbeke, 2010

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

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