European Copper Institute
Copper Alliance

Comments on the proposal for harmonized hazard classification of Copper, Granulated

FINAL - May 12, 2017

INTRODUCTION

The comments below reflect the views of the European Copper Institute (ECI). ECI represents the European copper industry all along the value chain: copper producers, recyclers, and manufacturers of semi-fabricated products.

These comments are also the views of:

- the International Copper Association
- the Copper Compounds Consortium
- the applicant Arch Timber Protection
- the European Metal Particulate Association, a Division of the German Aluminium Association

We are grateful for having the opportunity to comment on the harmonized hazard classification of "Copper, Granulated". We furthermore gratefully acknowledge and appreciate the alignment with the Copper Voluntary Risk Assessment, as well as the newly updated REACH registration data.

For most endpoints in the human health section, the data used and interpretation of the data reflect the hazard profiles previously agreed for nine other copper substances reviewed in 2014 for genotoxicity, reprotoxicity, carcinogenicity and STOT-RE (published in the subsequent RAC opinions and in the 9th ATP). However, for some endpoints, we have a different interpretation of the data presented in the CLH document and we have therefore focussed our comments on these endpoints and propose to revise the classification to **No classification warranted for acute eye irritation**[1]

Comments have also been provided on the on interpretation and use of the extensive copper ecotoxicological database. These are related to the need for guidance on "rapid removal" for inorganic substances, to the inclusion of recently obtained ecotoxicity studies at low pH, and to the methods used for data grouping. These comments result in **no classification for long-term environmental hazard.**

The detailed comments are shown below.

GENERAL COMMENT

1. We agree that *Copper, granulated* is a form of copper defined by its particle size and specific surface area, as mentioned on page 12. We suggest that, for clarity and in order to correctly reflect the scope of this dossier, the specific surface area should also be reflected in Table 1 (page 5) and Table 5 (page 10).

[1] CLH report proposal: Eye irritation Cat 2 – H318

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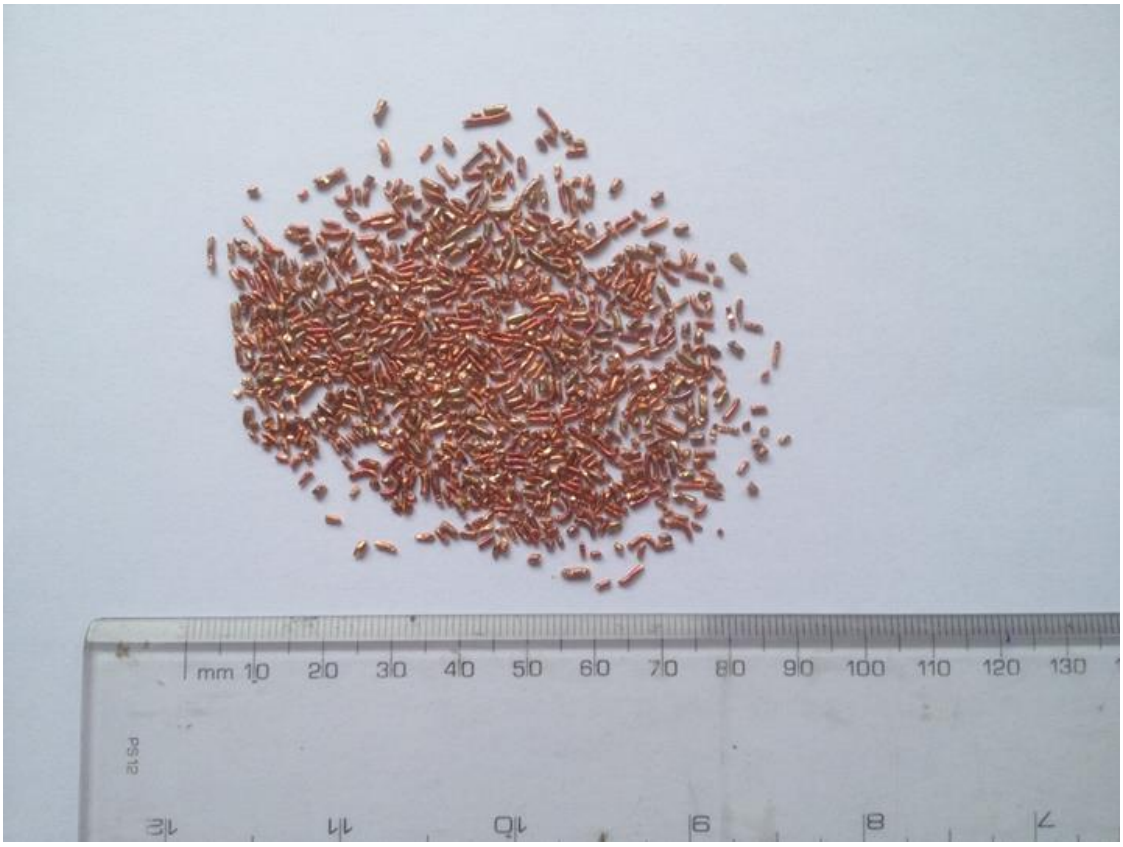
COMMENTS ON HUMAN HEALTH ENDPOINTS

2. Granulated copper is a form of copper defined by its particle size and specific surface area. This is shown in the photograph below for clarification of the physical nature of the substance. Due to the specific form of granulated copper, this substance is not suitable for testing in *in vitro*/*ex vivo* and *in vivo* eye irritation studies.



The OECD 405 eye irritation study states that for the testing of solids, "The test material should be ground to a fine dust. The volume of solid material should be measured after gently compacting it, e.g. by tapping the measuring container." This would be very difficult to achieve for granulated copper. The substance is clearly a very coarse material which on contact with the eye could be considered as a possible cause of physical trauma. However, it would quickly be physically removed by anyone exposed to the substance because of its relatively large size.

For the purposes of classification, read across based on solubility is possible with other copper compounds e.g. copper oxide, copper sulphate pentahydrate, dicopper oxide and coated copper flake, for which eye irritation studies are available. Comparison of available transformation-dissolution data and results of eye irritation studies are presented below:

Substance	T/D studies at pH 6 after 7 days (loading 1mg/L) Copper release µg/L	Results of OECD 405 *in vivo* eye irritation study
Granulated copper	1.4*	N/A
Copper oxide	49	Not Classified
Dicopper oxide	236	Classified
Coated copper flake	721	Classified
Copper sulphate pentahydrate	Fully soluble substance	Classified

*This value comes from the T/D study discussed on p 190 of the CLH document. As none of the other T/D studies conducted on copper oxide, dicopper oxide and coated copper flake took into account anti-abrasion measures, it was considered that the T/D study on granulated copper (ECTX 2016a) was more appropriate for this read across exercise.

It is therefore proposed that classification as an eye irritant for granulated copper is not warranted due to the specific form and size of granulated copper. Read across to other forms of copper/copper compounds also indicate that granulated copper should not be classified as an eye irritant based on solubility which could be an indicator of copper ion irritancy.

COMMENTS ON ENVIRONMENT ENDPOINTS

3. Regarding "rapid removal from the water column", the proposal states (page 140) that "*as there is no new guidance available about the "rapid removal concept" for metal compounds,* [new considerations on rapid removal] *were not further considered in this dossier.*" Indeed, there is a need for guidance on applying "rapid removal" to inorganic substances, in order to create a level playing field for all substances. The weight-of-evidence discussed in the copper REACH registration dossier shows that copper is rapidly removed from the water column for the purpose of hazard classification.

4. Regarding the species used for environmental classification (page 142-144), the proposal uses standardized methods, species, and endpoints as the basis for hazard classification of Granulated copper. We agree with the choices described for the selection of standard fish, daphnid and algae/plant species as described on page 143-144. This ensures that environmental hazard classification of substances is a comparative exercise, creating a level playing field for all substances. Furthermore, the ecotoxicity database of copper contains almost 800 acute and 200 chronic data points on standard species. Such a rich database allows to reliably derive a hazard classification.

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5. In 2014, RAC identified a lack of copper ecotoxicity data to fish at low pH. The classification proposal now includes recent fish chronic ecotoxicity data, which were added to the ecotoxicity database (pages 147, 154 and 155). We support the inclusion of these data on P. promelas and O. mykiss at low pH, generated by Oregon State University (OSU, 2016a and 2016b), for hazard assessment of copper. The toxicity thresholds show that the chronic sensitivity of both fish species does not largely differ between pH 6 and pH 7. For O. mykiss, the most sensitive endpoints at each pH resulted in EC_{10} values of 28.2 µg/L at pH 6 versus 38.8 µg/L at pH 7. For P. promelas, the various tests allowed to conclude that there is no significant relationship between pH and Cu toxicity over the range of pH conditions tested (Figure 1).

   In summary, the available data on 2 species show that the chronic sensitivity of fish at pH 6 is similar to that at pH 7.

   The proposal also considers that the OSU (2016b) data may replace the Ng et al. (2010) data for hazard classification (page 154). The O. mykiss data by OSU (2016b) were obtained under conditions similar to the Ng et al. (2010) study, but the OSU (2016b) data had real replicates and statistical assessment, organisms acclimated to low pH, and pre-equilibrated test waters. Therefore, we agree that the OSU (2016b) data can substitute for the Ng. et al. data. However, it should be noted that the Ng et al. data also confirmed that there were little or no sensitivity differences to fish between pH 6 and 7.

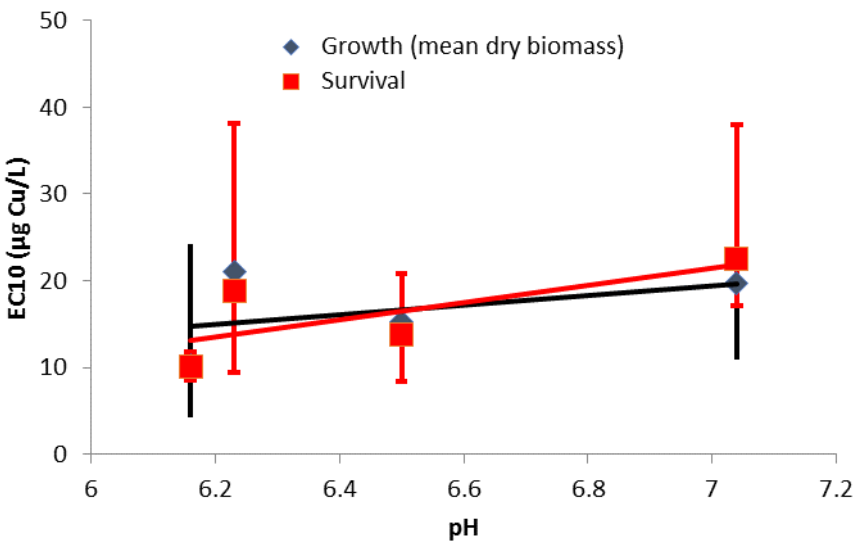

Figure 1: Chronic toxicity of copper to P. promelas *at various pH (OSU, 2016a and 2017)*

6. The proposal uses, in some cases, the lowest value when grouping ecotoxicity data in the same pH band and for the same endpoint (pages 146 and 191-192). Considering the CLP guidance, given the data-richness of copper, and given the multiple data available for the same species, we suggest the geometric mean can always be used for grouping data within the same pH band and for the same endpoint. The CLP guidance v. 4.1 (section 4.1.3.2.4.3., p. 500-501) specifies that data grouping must be dealt with on a case-by-case basis. *"When larger data sets (four or more values)*

are available for the same species, the geometric mean of toxicity values may be used as the representative toxicity value for that species." (CLP Guidance, v. 4.1, 4.1.3.2.4.3., p. 500-501). The CLP guidance does not mention that the use of geometric means would be restricted to cases with four or more values within each pH band.

The CLP guidance furthermore states that statistical techniques can be used in a weight-of-evidence approach when setting toxicity reference values for data-rich substances: "*In case of very large data sets meeting the criteria for applying the Species Sensitivity Distribution (SSD) approach (see IR/CSA, Chapter R.10), statistical techniques (e.g. HC5 derivation) can be considered to estimate the aquatic toxicity reference value for classification (equivalent to using the lowest EC50 or NOEC), in a weight of evidence approach.*" The copper ecotoxicity dataset is extremely data-rich, with close to 800 acute and 200 chronic data points for standard species for hazard classification. However, following the criteria mentioned in Chapter R.10, there are insufficient standard species to use an SSD approach. It seems therefore not straightforward to apply this technique for copper hazard classification.

A statistical technique that can be used more easily for copper hazard classification, is bootstrapping. This method was used to simulate the outcome of a hazard assessment if copper would be a data-poor substance. One acute and one chronic data point was randomly selected for each taxonomic group, and the corresponding acute and chronic ERVs were determined. This statistical technique was repeated 2000 times and results in a probabilistic distribution of ERVs for copper. The median value of such distribution represents the most likely ERV (and associated classification) if copper would have been a data-poor substance (cfr. the data-poor approach for inorganic sparingly soluble metal compounds). The bootstrapping analysis resulted in an expected acute ERV of 29.4 µg/L and a chronic ERV of 13.8 µg Cu/L. These values are more than a factor of two above some of the ERVs put forward in the classification proposal. Hazard classification should create a level playing field for all substances, and data-rich substances should not be classified more stringently than data-poor substances.

Given the weight of evidence, and referring to the "case-by-case assessment" for data-rich substances mentioned in the CLP guidance, it is appropriate to always use the geometric means to group the data within each pH band and endpoint. The following comments specifically address how the ERVs change based on this approach. Table 1 below provides an overview of the critical cases where the method for data grouping influences the ERV.

6.1. The proposed acute ERV at pH 7 (page 187) was derived for D. rerio. In total, there are 5 values available for D. rerio across all pH bands. Therefore, the geometric mean can be used for grouping the data within each pH band, as reported in the white lines of Table 90 (page 187) of the classification proposal. This means that, within the pH 7 band, the value for D. rerio should be calculated as the geometric mean of two available values (11.7 and 35 µg/L), which equals 20.24 µg/L. Likewise, within the pH 8 band, the value for D. rerio should be calculated as the geometric mean of three available values (148.4, 149, and 212.1 µg/L), which equals 167.4 µg/L.

It must furthermore be noted that ample data on the acute toxicity of copper to other fish species are available, with a very high number of data points across all pH bands (P. promelas, 258 data points, and O. mykiss, 77 data points).

Therefore, the acute ERV at pH 7 should be 14.0 µg/L (*C. dubia*, geometric mean of 17 values).

6.2. The proposed chronic ERV at pH 6 (page 188) of 8.7 µg/L (endpoint: growth, lowest value out of 3 values) is based on P. promelas data [2]. In total, there are 35 values available for P. promelas across all pH bands, and 13 values for the growth endpoint alone. Therefore, the geometric mean can be used for grouping the *P. promelas* data within each pH band.

This is further substantiated by the observation that the chronic sensitivity of fish to copper does not strongly differ between pH 6 and 7 [3].

Furthermore, an additional P. promelas chronic study at pH 6 has been conducted at Oregon State University for this species (OSU, 2017). The study OSU, 2017 was additionally obtained in March 2017. Its experimental setup was identical to the OSU, 2016a study, but the exposure concentrations were different in order to avoid the unbounded toxicity thresholds reported in OSU, 2016a. The OSU, 2017 data have not yet been included in the classification proposal by the competent authority or in the REACH registration dossier of copper, and therefore the study report is provided as confidential attachment to these comments. The reported EC10 values are 18.9 µg/L for mortality and 25.2 µg Cu/L for growth (as mean dry weight). By adding these two new values to the chronic data set, the geometric mean values are now based on four values, and can therefore replace the lowest value. The geometric mean values for mortality and growth are now 13.3 µg Cu/L and 13.9 µg Cu/L, respectively.

The chronic ERV at pH 6 then becomes 13.2 µg/L (*D. magna* reproduction; geometric mean of 7 values).

6.3. The proposed chronic ERV at pH 7 is 5.9 µg/L, based on P. promelas (endpoint mortality, lowest value out of 3 data points), closely followed by S. fontinalis (6.4 µg/L, endpoint reproduction, lowest value out of 3 data points) (page 188).

6.3.1. For P. promelas, there are in total 35 values available across all pH bands, and 11 values for the mortality endpoint alone. The proposed value of 5.9 µg/L stands out compared to all other values at different pH and for different endpoints. In addition, the chronic sensitivity of fish to copper does not strongly differ between pH 6 and 7 (see footnote 3). Given the weight of evidence, the geometric mean should be used for grouping P. promelas mortality data within the pH 7 band. The geometric mean

[2] The value of 8.7 µg/L is the NOEC for growth (as mean dry weight) reported by OSU (2016a), but there is a reliable EC10 value available of 9.0 µg/L (confidence limits 4.5-18 µg/L). Therefore, the EC10 of 9.0 µg/L is preferred.

[3] As weight of evidence, it should be noted that, if all P. promelas data at pH 6 and 7 are pooled, this results in geometric mean values of 12.7 µg/L (mortality, n = 7), and 12.9 µg/L (growth, n = 8).

for P. promelas at pH 7 is 12.0 µg/L (mortality, n=3) as reported in Table 91 of the classification proposal.

6.3.2. For S. fontinalis, there are in total 11 values available across all endpoints within the pH 7 band. An additional study on reproduction of S. fontinalis reports unbounded NOECs (no effects on reproduction at the highest concentration of 9.4 µg Cu/L, McKim and Benoit, 1974). Due to uncertainty related to the pH during this test, it should normally not be used for deriving the ERV. The data can, however, be used as supporting information to justify the use of a geometric mean. The geometric mean for reproduction of S. fontinalis at pH 7 becomes 15.9 µg/L (n=3), or 14.0 µg/L (n=4) if the unbounded NOEC from McKim and Benoit is used.

With the above considerations, the chronic ERV at pH 7 becomes 12.0 µg Cu/L (P. promelas, growth and mortality).

Table 1: overview of critical toxicity data for species and endpoints with two or three available data points within each pH band

Species	Endpoint	pH band	Lowest value proposed by eCA	Geometric mean proposed by eCA	Revised geometric mean (with considerations in this document)
D. rerio	Acute mortality	>6.5-7.5	11.7 µg Cu/L	20.24 µg Cu/L (n=2)	20.24 µg Cu/L (n=2)
P. promelas	Chronic Mortality	5.5-6.5	10.1 µg Cu/L	11.8 µg Cu/L (n=3)	**13.3 µg Cu/L (n=4)**
P. promelas	Chronic Growth	5.5-6.5	9.0 µg Cu/L[(1)]	11.4 µg Cu/L (n=3)	**13.9 µg Cu/L (n=4)**
P. promelas	Chronic Mortality	>6.5-7.5	5.9 µg Cu/L	12.0 µg Cu/L (n=3)	12.0 µg Cu/L (n=3)
P. promelas	Chronic Reproduction	>6.5-7.5	10.8 µg Cu/L	13.14 µg Cu/L (n=2)[(2)]	13.14 µg/L (n=2)
S. fontinalis	Chronic Reproduction	>6.5-7.5	6.4 µg Cu/L	none	**15.9 (n=3) or 14.0 µg Cu/L (n=4)**

[(1)]: Table 76 in the proposal document erroneously reports a lowest value of 8.7 µg Cu/L; this value is the NOEC, whereas the EC_{10} is 9.0 µg/L. Table 75 of the proposal document (Table that contains all individual data) only reports the EC_{10} value of 9.0 µg/L

[(2)]: Table 76 in the French proposal document reports a geometric mean of 17.3 µg Cu/L, but the geometric mean of two values (10.8 and 16 µg/L) equals 13.14 µg/L, as reported in Table 91.

7. We agree with the transformation-dissolution approach used in the proposal (page 190-191): surface area-based transformation-dissolution data that are obtained with granulated copper as test substance, and the use of the measured specific surface area of the substance to calculate the metal release after 7 and 28 days. The metal release per unit surface is an intrinsic property of the material.

8. We support comparison of the transformation-dissolution data and the ERV at the same pH (page 191), which is in accordance with the CLP guidance (section IV.2.3, p. 586). However, based on the ERVs derived as discussed above, the conclusion should be "no classification" (Table 2).

Table 2: classification of granulated copper for environmental hazards, based on ERVs at different pH bands compared to transformation-dissolution data.

ACUTE	**ERV (µg Cu/L)**	**Transformation-dissolution at 1 mg/L loading after 7 days**	**Classification**
pH 5.51-6.5	12.1	3.4	No
pH 6.51-7.5	**14.0**	2.3	No
pH 7.51-8.5	40.0	1.2	No

CHRONIC	**ERV (µg Cu/L)**	**Transformation-dissolution at 1 mg/L loading after 28 days**	**Classification**
pH 5.51-6.5	**13.2**	13	No
pH 6.51-7.5	**12.0**	8.6	No
pH 7.51-8.5	12.6	4.9	No

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REFERENCES

McKim, James M., and Duane A. Benoit. "Duration of toxicity tests for establishing no effect concentrations for copper with brook trout (Salvelinus fontinalis)." Journal of the Fisheries Board of Canada 31, no. 4 (1974): 449-452.

Ng, T., Chowdhury, M. J., Wood, C. M. (2010). Can the Biotic Ligand Model Predict Cu Toxicity Across a Range of pHs in Softwater-Acclimated Rainbow Trout? *Env. Sci. Technol.* 44, 6263-6268.

Oregon State University OSU, 2016a. Short-term chronic toxicity of copper to the fathead minnow, Pimephales promelas, under varying pH conditions. Report to the European Copper Institute, October 2016.

Oregon State University OSU, 2016b. Early life-stage toxicity of copper to the rainbow trout, Oncorhynchus mykiss, under varying pH conditions. Report to the European Copper Institute, October 2016.

Oregon State University OSU, 2017. Short-term chronic toxicity of copper to the fathead minnow, Pimephales promelas, at a pH of 6. Report to the European Copper Institute, March 2017.

Explanatory note: The studies OSU, 2016a and OSU, 2016b are included in the classification proposal by the competent authority and in the REACH registration dossier of copper. The study OSU, 2017 was additionally obtained in March 2017. Its experimental setup was identical to the OSU, 2016a study, but the exposure concentrations were different in order to avoid unbounded toxicity thresholds. Because they were only available very recently, the OSU 2017 data have not yet been included in the classification proposal by the competent authority or in the REACH registration dossier of copper.