ECHA consultation on proposed harmonised classifications for some copper compounds (19/12/13-03/02/14)
CLEAPSS points re proposal for Acute Toxicity (inhalation) 2 for copper(II) oxide
http://www.echa.europa.eu/harmonised-classification-and-labelling-consultation

The proposed harmonised classification: Copper(II) oxide

H statements: H330 Fatal if inhaled (CLEAPSS highlighting), H410 (environmental hazards)
Pictograms: GHS06 ('skull & crossbones), GHS09 (environmental hazard)
Signal word: Danger.

http://www.echa.europa.eu/documents/10162/64402c74-1625-47e8-9cf9-553e12b07f7b

Several reports and other documents are available via the ECHA website.

In 2006, ***Derogation and classification proposals for acute inhalation toxicity of copper powder, copper oxide, copper sulphate pentahydrate*** was published. This details the properties of the forms and compounds of copper, including solubility, airborne particle size and toxicokinetics. The paper makes a case for derogating copper(II) oxide from the requirement for animal testing and also from classification for acute toxicity by inhalation. Under section ***7 Derogation and classification proposals/7.1 Copper(II) oxide*:**

> The following conclusions are drawn from the data presented in this document:
> - Copper (II) oxide has a moderate (but not negligible) tendency to become airborne,
> - however, based on particle size considerations (MMAD > 60 µm), more than 95% of the material deposited in the respiratory tract will be translocated to the GI tract shortly after inhalation, so that the acute toxicity will be determined by that of the oral route,
> - Copper (II) oxide is assumed to have a low bioavailability, based on water solubility and on indicative data from animal feeding studies,
> - it has an established low oral toxicity (LD50 > 2000 mg/kg bw).
>
> It can therefore be concluded that the inhalation hazard of Copper (II) oxide is very low. It is therefore proposed to derogate from animal testing. In consideration of the arguments set forth above, a classification for acute inhalation toxicity is not required. (CLEAPSS highlighting)

In 2007, ***European Union Risk Assessment Report: COPPER, COPPER II SULPHATE PENTAHYDRATE, COPPER(I)OXIDE, COPPER(II)OXIDE, DICOPPER CHLORIDE TRIHYDROXIDE: CAS No: 7440-50-8, 7758-99-8, 1317-39-1, 1317–38–0, 1332-65-6; EINECS No: 231–159–6, 231–847–6, 215-270-7, 215–269–1, 215-572-9: VOLUNTARY RISK ASSESSMENT* (distribution date 1 June 2007),** collated data and information from a wide range of sources is presented. Much of the data and conclusions quoted in the harmonised proposal are detailed in this document. However, for Acute toxicity (inhalation) for copper(II) oxide/copper(II) hydroxide, none of the rat studies quoted in the proposals for harmonised classification (see overpage) are mentioned. Under ***Absorption in animals/inhalation*** (page 7), one animal study is described and it states:

> This study demonstrates the potential for systemic absorption of copper following inhalation of dust containing an unspecified amount of copper, but provides no reliable quantitative data which are relevant to human risk assessment.

In the absence of human data, MPPD modelling was carried out. The conclusions are that exposure of workers in a range of industrial contexts are not of concern so long as suitable respiratory protection is employed. On page 45:

> … Consideration of the available information against EU classification criteria leads to the conclusion that copper (II) oxide and copper powder do not require classification for acute inhalation effects. (CLEAPSS highlighting)

Comments were published by the European Copper Institute in 2008: ***Opinion of the TC NES on the Human Health Part of Industry Voluntary Risk Assessments on Copper and Copper compounds*** **(08/02/2008)**
In this document:

> UK expressed concerns linked to evidence of irritation as a local effect for some copper compounds since all the human data is based on oral exposure and there are uncertainties about effects following exposure by inhalation.

In the current proposal, other research seems to be presented. ***CLH report Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 Substance Name: Copper (II) oxide or cupric oxide or copper oxide*** **(12/07/2013)**
http://www.echa.europa.eu/documents/10162/64402c74-1625-47e8-9cf9-553e12b07f7b

explains how the assessment of the acute toxicity (inhalation) risk was derived for this proposal. A comparison with copper(II) hydroxide is made in the section on inhalation studies, and a decision to employ read-across to studies on that compound is recorded:

> ***Inhalation studies*:**
> No data are available on acute inhalation toxicity of copper (II) oxide in animals. But several salts of copper are classified for acute inhalation endpoint. In this context, a read across with an other salt was proposed.
> It was stated in VRA that acute inhalation toxicity of a substance could be determined to a large extent by solubility. Other physico/chemical properties may also be involved. …
> It was observed that Cu(II)O has a solubility very closed of CuOH at different pH. Moreover, CuOH and Cu(II)O have molecular mass roughly similar. And the two salts are made up of copper under the same state of oxidation (Cu2+). In this context, a read across between CuOH and Cu(II)O for acute inhalation endpoint was proposed .
> Copper Hydroxide requires a classification Acute Tox.2-H330 under CLP regulation.
> In this context, a classification Acute Tox.2-H330 under CLP regulation is also proposed for copper (II) oxide.

However, the data upon which the inhalation hazard classification for copper(II) hydroxide of H330 does not appear (to us at CLEAPSS) to be overwhelmingly strong. The proposal document for copper(II) hydroxide**:** ***CLH report: Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 Substance Name: Copper (II) Hydroxide or Copper Hydroxide or Copper Dihydroxide or Cupric Hydroxide*** **(12/07/2013)**
http://www.echa.europa.eu/documents/10162/c14572c9-08bb-44ee-b807-c2d480ced8a4

discusses the evidence for copper and its compounds to provoke metal fume fever (page 23):

> The conclusion of Borak et al was that, based on the seven studies identified in the literature search, there is insufficient evidence to conclude that exposure to copper dust or fume causes MFF. Based on data which are currently available, this conclusion would appear to be justified.

The proposal paper also presents data for 3 studies on rats, one which was not standard or totally reliable. The other 2 studies yielded the following results:

Chevalier (2003):	~0.205<LC_{50}<1.08 mg/L air
Rush (1992):	LC_{50} (male) = 0.5 mg/L air
	LC_{50} (female) = 0.61 mg/L air

Section ***4.2.4 Comparison with criteria*** states:

> The inhalation LC_{50} lies within the range (0.05-0.5 mg/l) for classification as Acute Tox. 2 (H330: Fatal if inhaled) under regulation (EC) 1272/2008. (page 33)

The inhalation LC_{50} range for classification as Acute Tox. 3 (H331: Toxic if inhaled) is (0.5-1.0 mg/l). The data appear to fall closer within this range, though considering the other data presented, we wonder whether even this classification can be justified.

CLEAPSS comments
The above data appear to fall towards, and some even above, the higher end of the classification bracket for classification as Acute Toxicity 2 for inhalation.
In view of this, as well as the sparsity of evidence of inhalation risk in mammals, the lack of human data and conclusions in the other references above, CLEAPSS does not agree that such a classification is justified. We suggest that even a classification of Acute Tox. 3 may not be fully justified.