SIDS INITIAL ASSESSMENT PROFILE

Category Name	Copper and copper compounds
CAS No(s) and chemical name	CAS 7440-50-8 (copper powder and massive[1]) CAS 7758-99-8 (copper sulphate pentahydrate) CAS 1317-38-0 (copper oxide) CAS 1317-39-1 (dicopper oxide) CAS 1332-65-6 (dicopper chloride trihydroxide)
Chemical Formula(s)	Cu $CuSO_4.5\ H_2O$ CuO Cu_2O $Cu_2Cl(OH)_3$

SUMMARY CONCLUSIONS OF THE SIAR

This document covers the category assessments for copper metal, massive and powder, coated copper flakes and several copper compounds, assessed under the EU Risk Assessment. Substance specific aspects are provided where relevant.

The SIAR is based on the EU Risk Assessment of copper and various copper compounds used as general chemicals, under the Existing Substance Regulation, completed in 2008 as an industry initiative. The copper risk assessment report and opinions from EU technical and scientific committees are available from *http://echa.europa.eu/copper-voluntary-risk-assessment-reports.* Considering the comments from the EU technical and scientific committees and additional information obtained from industry, updates were done for the 2010-2013 REACH registrations and this SIAR. Nevertheless, a limitation of this SIAR is the small number of recent open literature data (beyond 2006).

Rationale for copper category approach

The category includes a group of commonly used copper substances whose ecotoxicological and systemic human hazard profiles are related to the release of copper-ions. Nanoform copper substances are excluded from this assessment because the biological effects of nanoform metals can differ from the ionic forms.

The category includes five substances: soluble copper sulphate pentahydrate and dicopper chloride trihydroxide, less soluble CuO and Cu_2O, and three forms of zero valent copper materials (Cu°): copper massive, copper powder and coated copper flakes[2,3]. Coated copper flakes are added to the category because human health haz-

[1] Includes copper flakes, coated with aliphatic acid, because the toxicity data on this material is used to read across to copper powders and massives. The same CAS number is thus used to cover three different forms of copper in this assessment (massive, powder and coated flakes).

[2] Aliphatic acids are added for the production of coated copper flakes, to stabilise the copper flake in small particle sizes with higher surface area (needed for specific niche applications – biocides and pigments).

ards are available for these coated copper flakes. Where relevant for read-across purposes, information from other copper compounds is included in the assessment.

For the environmental endpoints and systemic health endpoints, the copper ion is considered as the reactive functional group within the category. The counter-ions of the copper salts (i.e. oxygen, sulphate, chloride and hydroxide), are due to their ubiquitous presence in environmental media and human fluids not considered to contribute to the environmental nor systemic human toxicity of copper salts.

The category implies that the effects assessment is expressed as Cu-ions and that further read-across to other copper compounds, not assessed in this SIAR, is possible on condition that the copper ions are driving the toxicity.

Copper is an essential nutrient for humans and non-human organisms and, therefore, low concentrations may lead to deficiency while high concentrations of copper ions may lead to copper toxicity.

Once released to the environment, copper ions have more than one oxidation state. The principal ionic forms are cuprous (Cu(I), Cu^{+}) and cupric (Cu(II), Cu^{2+}). The trivalent form (Cu(III), Cu^{3+}) occurs but is relatively unimportant in physical and biological systems. Cu^{+} is unstable in aqueous media and Cu^{1+}-ions readily transform into Cu^{2+}-ions. Depending on the chemistry of the receiving environment, soluble and/or insoluble copper compounds are formed. Hence Cu^{1+}-ions are, due to their instability, considered as a source of Cu^{2+} ions for environmental and systemic toxicity.

Environment:

The assessment aims at defining the basic hazards profile of soluble and sparingly soluble compounds, copper metal (powder and massive forms) and coated copper flakes.

Human health:

The human health hazard assessment addresses a large variety of effects and different administration routes. In assessing the human health effects of copper and copper compounds, the essentiality and homeostatic mechanisms have to be considered.

Acute effects are based on tests with the individual substances. Short term and long term systemic effects are based on tests with the individual soluble substances belonging to the category and/or read-across where such data are not available

Physical-chemical properties

Physico-chemical properties that are important for the human health and environmental hazard profiles are granulometry and solubility.

- Copper metal (Cu°) is insoluble and needs to be transformed to Cu(I) or Cu(II) to become bio-available/bio-accessible. Typical copper powders have a diameter of around 100 µm but small production volumes of fine powders are also reported. The surface area of fine powders (10-50 µm) is 67-107 mm^2/mg. The surface area of a massive copper material (sphere of 1 mm) is 0.67 mm^2/mg. The melting point of copper metal is 1059 - 1069°C. Its boiling point has not been determined in view of the high melting point.

[3] The same CAS number is used to cover three forms of zero valence copper materials : massive, powders and coated copper flakes.

- Copper flakes, coated with aliphatic acids have a particle size of 8 – 11 µm and surface area of 2,900 mm^2/mg. Cu is in the form of Cu° and therefore needs to be transformed to Cu(I) or Cu(II) to become bio-available/bio-accessible. The melting point of coated copper flakes is 1057 - 1058°C. Its boiling point has not been determined in view of the high melting point.

- Copper sulphate pentahydrate is a blue crystalline powder. Its water solubility at 25°C is 220 g/L. Copper sulphate pentahydrate decomposes at 110°C without melting or boiling.

- Dicopper oxide is an orange-red powder. The water solubility at 20°C is ≥ 28.6 g/L at pH 4.0, 6.39×10^{-4} g/L at pH 6.5 - 6.6, and < 5.39×10^{-4} g/L at pH 9.8. The melting point of dicopper oxide is in excess of 400°C (the maximum temperature tested). Its boiling point has not been determined in view of the high melting point.

- Copper oxide is a dark grey powder. The water solubility at 20°C is > 0.23 g/L at pH 5.1 - 5.5, 3.94×10^{-4} g/L at pH 6 and < 1.0×10^{-5} g/L at pH 9. The melting point of copper oxide is 1326°C. Its boiling point has not been determined in view of the high melting point.

- Dicopper chloride trihydroxide is a light green powder. The water solubility at 20°C is > 101 g/L at pH 3.1, 1.19×10^{-3} g/L at pH 6.5 and ≤ 5.25×10^{-4} g/L at pH 10. Dicopper chloride trihydroxide decomposes from 240°C without melting or boiling.

Remark 1: The octanol-water partition coefficient (log K_{ow}) is not relevant (the mechanisms of absorption of Cu^{2+} into organic matter and living cells are different from those traditionally attributed to carbon-based substances and the parameter therefore has little relevance to ionic copper). pKa is also not considered a relevant parameter and is thus not mentioned above.

Remark 2: Data on vapour pressure are only relevant for coated copper flakes (7.5e-9 Pa (20°C), they are negligible for Cu-compounds and Cu-metal. Vapour pressure is therefore considered as not relevant to the category members

Essentiality

Copper is an essential micronutrient, needed for optimal growth and development of micro-organisms, plants, animals and humans.

Human Health

Toxicokinetics (absorption, metabolism, distribution and elimination)

Introduction

The toxicokinetics of essential elements such as copper are regulated to a large degree by homeostatic mechanisms. Homeostasis can be described as the maintenance of a constant internal environment in response to changes in internal and external environments. Homeostatic maintenance requires the tightly coordinated control of copper uptake, distribution and efflux in cells and the organism as a whole. As a result of the presence of a homeostatic mechanism for copper, rat and human metabolism of copper are very similar and are therefore discussed together in the following sections.

Essentiality

Copper is an essential metal present in human body tissues and fluids at concentrations of parts per million or parts per billion. In common with other trace metals, copper has a number of physiological roles that may be classified as regulatory, structural and/or protective. In the regulatory role they are an essential part of metal-

loenzymes, acting either as electron donors or acceptors at the active site, or by shaping the enzyme to the configuration necessary for its activity. The structural functions of trace metals may be in, for example, membrane integrity or bone structure, and the protective function may involve antioxidant defence or the immune system. Copper is involved in the reactions and functions of many enzymes, including angiogenesis, neurohormone release, oxygen transport and regulation of genetic expression. Copper is an allosteric component of several enzymes that have oxidation and reduction activity, functioning as an electron transfer intermediate in redox reactions.

Absorption

Oral

A large quantity of oral absorption data are available for animals, specifically rats, and humans. These data enable an estimation of true absorption at the relatively high copper intakes used in toxicity studies.

True absorption was determined as there is a large quantity of data available on the absorption of copper in animals and humans, predominantly relating to oral exposure. In these studies, quantitative data on the absorption of copper have been based on faecal monitoring, as faecal excretion is the main excretory route for copper. In several of these studies, the amount absorbed has been determined as the difference between oral intake and faecal excretion. This absorption value represents a measure of *apparent absorption* only, as faecal copper does not distinguish between unabsorbed copper and endogenous copper losses. Endogenous copper losses may occur from (1) biliary excretion of systemically-absorbed copper that mixes with the endogenous pool and is subsequently excreted, and (2) the fraction absorbed by intestinal mucosa and subsequently eliminated into the GI tract as cells are sloughed off (i.e. without systemic absorption). *Apparent absorption* thus represents a somewhat crude measure of copper absorption. In order to measure *true absorption*, which provides a more accurate measure of copper absorption following oral exposure, the percentage of copper intake recovered in the faeces was corrected for endogenous copper losses.

Based on these absorption data, an absorption factor of 25% is taken to be the best estimate of true absorption in rats at the high copper intakes.

The most reliable human data currently available on copper absorption following oral exposure come from volunteer studies. Based on the available true absorption data, oral absorption rates in humans have been derived.The available data have been fitted to two functions giving a continuous distribution with mostly similar results:

Equation 1: oral absorption% = -15.0 ln(x) + 63.2777

Equation 2: oral absorption% =72.287 $e^{-0.1167x}$

x= copper intake (mg/day)

For a given dose in the GIT, absorption in humans is calculated based on the mean result for these two functions. In humans, this method of calculation is applied to the sum of the oral intake and copper arising from inhalation exposure and subsequently translocated to the GIT. The minimum oral absorption is set to 20%.

Oral absorption data for humans and rats show qualitative and quantitative similarities between the two species. In both species, absorption of copper over the range of intakes studied is inversely related to copper intake, illustrating the important role of absorption in copper homeostasis. In both species, true absorption of copper from diets containing what are considered as adequate levels of copper (1-10 mg/day in humans; 0.3-0.6 mg/kg bw/day in animals) is in the 30-60% range. The above oral absorption data, and corresponding functions, are based on copper sulphate. Assuming that orally-administered copper will occur in the GIT, at least in part, in the ionic form and therefore be available for absorption, and in view of the solubility of copper sulphate, it is considered appropriate to adopt a conservative approach and to use the oral absorption data for cop-

per sulphate for other less soluble copper species.

Dermal absorption and penetration

In the two reviewed studies, the copper compounds were applied in an aqueous medium (suspension). There is uncertainty about the applicability of these absorption data to exposures of dry copper compounds as encountered in occupational exposure scenarios. However, in view of the limitations of the studies on which this dermal absorption factor is based (absence of mass balance data and large standard deviations); the value of 0.3% is considered to represent the best estimate based on data currently available.

Given the available studies provide no consistent evidence that dermal absorption is greater for soluble than for insoluble copper substances, a dermal absorption factor of 0.3% is also proposed for both soluble and insoluble copper substances.

For dry exposure scenarios, a 10-fold lower dermal absorption value is proposed (0.03%), consistent with the approach used in the OECD Cooperative Chemicals Assessment of Zinc (and EU risk assessment).

Distribution

On entering interstitial fluid and blood plasma, absorbed copper initially becomes bound to two proteins, albumin and transcuprein. Most of the copper bound to albumin and transcuprein is rapidly transported via portal blood to the liver. Once in the liver, copper is incorporated into ceruloplasmin, which is subsequently released into the systemic circulation for delivery to other tissues.

Excretion

Quantitative data on excretion were reported in a bioequivalence study. The fate of excess copper was examined in bile-cannulated male Sprague Dawley rats (five per group) following oral administration of a single dose of copper (nominal dose 20 mg Cu/kg bw; actual dose 22-24 mg Cu/kg bw). Six inorganic copper salts were investigated including three category members. Copper levels in excreta during the 24-h period after dosing were as follows: bile 1.54-2.48% of dose; urine 0.20-0.39% of dose; faeces 64-76% of dose (although it is noted that faecal copper will also comprise some absorbed copper). Values were found to be similar for all six substances tested. The results showed faecal excretion to be the main route of elimination for orally-administered copper, with urinary excretion as a relatively minor route.

Comparative bioavailability

In mammalian toxicity, it is also considered that the most toxic form of any copper salt is the Cu^{2+} ion. This can be shown through the comparison of the most soluble (e.g. copper sulphate pentahydrate, copper nitrate) and relatively insoluble copper salts, where the solubility, bioavailability and hence toxicity of these salts can vary – with copper sulphate pentahydrate representing the worst-case scenario. As all suitable short- to long-term available animal copper toxicity studies are derived from oral administration, the use of copper sulphate pentahydrate data would represent a worst case scenario for the determination of the effect of relatively insoluble copper compounds in mammalian toxicity. In addition, the use of copper sulphate pentahydrate data would minimise the number of animal studies.

In vivo bioavailability

For the oral exposure route, in a series of bioavailability studies, conducted by several authors the bioavailability of copper sulphate to other relatively insoluble copper salts including copper oxide was compared. 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 absorption from the gastro-intestinal tract, namely the liver and bile.

Relative bioavailability of supplemental copper sources

Source of copper	Species		
	Poul-try	Swine	Cattle
Copper sulphate	100	100	100
Copper oxide	0 (3)	30 (4)	15 (2)

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

The low bioavailability of copper in copper oxide, relative to that of copper in the sulphate salt, was also demonstrated in the rat following administration at adequate dietary levels.

In vitro bioavailability

Several studies assessed the release/dissolution of metal ions from metal bearing materials (minerals, soils, substances) in simulated biological fluids.

The release/dissolution of copper ions from copper materials and copper compounds was assessed from *in vitro* tests using biological fluids simulating oral exposure. The *in vitro* tests follow the ASTM D 5517-07 protocol, using HCl 0.07N (pH 1.5) as a gastric mimetic fluid. The copper materials tested include: copper wires (representing massive copper materials), copper powder (130 µm median diameter), biocidal and non-biocidal coated copper flakes (ca 8.5 µm), copper oxide, cuprous chloride and dicopper sulphide. Loading rates between 100 mg/L and 2 g/L were assessed. The results are expressed as % copper dissolved at the end of the bioelution test.

Copper, in the form of Cu°, is insoluble and needs to be transformed to Cu^{+} or Cu^{2+} to demonstrate solubility. Such transformation/dissolution takes place at the surface of the copper particles and therefore, for the copper massive, copper powder and coated copper flakes, the influence of surface area on bioaccessibility was also evaluated.

The results are summarized in the Table below. All copper present in $CuSO_4$ was solubilised (99.95%) in the gastric fluid while "massive" copper materials, tested as wires at different mass loadings (59 to 478 mg/L) and surface loadings (67 – 516 mm^2/L) consistently showed low solubility (0.1%).

Relative bio-accessibility of copper and copper compounds, assessed from the recovery of copper after bioelution tests in gastric fluids (pH 1.5, 2 hours) in accordance to ASTM D 5517-07.

Material Tested	Composition	Bioelution recovery (as % of Cu content)
Cu massive	>99.9% Cu	0.096 – 0.105
Cu powder	99.7% Cu, 0.3% Cu_2O	1.1 – (7.3*)
Dicopper sulphide	79.9% Cu	3.3

Cu flake – biocidal product	93.7% Cu, 2.6% Cu_2O, 3.89% LOI**	42 – 71
Cu flake – non-biocidal product	96.3% Cu, 1% Cu_2O, 2.8% LOI**	44 – 60
CuCl	63.78% Cu	77 – 94
CuO	80% Cu	68-84%
$CuSO_4$	25.45% Cu	100

*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 if ignition, as a measure of the organic content (coating by aliphatic acid).

For the Cu° materials, the relation between the release of Cu-ions and the surface area exposed is well described by a power function:

Bioaccessible copper ions = 1.94 surface loading (mm^2/L) $^{0.84}$

In conclusion, the *in vitro* gastric bioelution tests with various copper-bearing materials demonstrate important differences in bio-accessibility in gastric fluids: $CuS0_4.5H_20$ (100%) > CuCl > CuO > coated copper flakes > Cu_2S > copper powder > copper massive (0.1%).

The data also show that bio-accessibility of Cu° is related to surface area, described by the power function. Measured and modelled (from the power function) bio-soluble copper concentrations released from 200 mg copper powders/L are respectively 1.1% and 2.8% for a typical copper powder (0.024 m^2/g) and reasonable worst case 10 µm powder (of 0.067 m^2/g). Using the coated copper flakes as reference substance (with average bio-accessibility of 57%), the relative bio-accessibility of a typical copper powder (0.024 m^2/g) and reasonable worst case 10µm powder (of 0.067 m^2/g) are therefore respectively 1.9% and 4.9%.

These data can be used to predict the acute oral toxicity of copper massive and copper powder using available toxicity studies on other forms of copper and copper compounds and this is presented below in the acute toxicity section.

Acute toxicity

Available key study data for acute toxicity:

Key studies for acute toxicity by inhalation, dermal and oral exposure route

Route of administration / endpoint / test guideline	**Test substance**	**Clinical effects**	**Endpoint value**
Inhalation (US 173.132)			
LC_{50}, rat (m/f) – nose only	Dicopper chloride trihydroxide		>11.4 mg/L air (m/f)
Inhalation (OECD 403)			
LC_{50}, rat (m/f) – nose only	Dicopper chloride trihydroxide		2.83 mg/L air (m) > 2.77 mg/L air (f) 4.74 mg/L air (m/f)

LC_{50}, rat (m/f)	Dicopper oxide	Lung abnormalities, wet fur, staining, hunched posture, piloerection, ptosis, altered respiration.	2.92 mg/L air (m) 3.69 mg/L air (f) 3.34 mg/L air (m/f)
LC_{50}, rat (m/f)	Dicopper oxide	Respiratory depression, discolored lungs.	5.36 mg/L air (m/f)
LC_{50}, rat (m/f)	Dicopper oxide	Apathy, sedation, difficult respiration, squat position, reduced reflexes, tremors, disturbed coordination.	> 30 mg/L air (m/f)
LC_{50}, rat (m/f)	Dicopper oxide		> 5 mg/L air (m/f)
LC_{50}, rat (m/f)	Dicopper oxide	Respiratory reduction, enlarged lungs, subdued, hunched posture, piloerection, hypothermia, ataxia, staining of the fur, discoloration perianal region, slightly emaciated and unkempt condition. reduced weight gain.	ca. 5 mg/L air (m/f)
Inhalation (OECD 436)			
LC_{50}, rat (m/f)	Coated copper flakes	Ataxia, tremor, dyspnoe, reduced motility, reduced body weight gain. Grey-stained discolored lungs.	> 5.11 mg/L air (nose only-dry aerosol)
LC_{50}, rat (m/f)	Coated copper flakes	Decreased respiratory rate, laboured respiration, noisy respiration, hunched posture, piloerection	Males 0.733 mg/L Female 1.67 mg/L
Dermal (OECD 402)			
LD_{50}, dermal, rat (m/f)	Coated copper flakes		> 2,000 mg/kg bw
LD_{50}, dermal, rat (m/f)	Copper oxide	None	> 2,000 mg/kg bw
LD_{50}, dermal, rat (m/f)	Copper sulphate pentahydrate pentahydrate		> 2,000 mg/kg bw
LD_{50}, dermal, rat (m/f)	Dicopper chloride trihydroxide		> 2,000 mg/kg bw
LD_{50}, dermal, rat (m/f)	Dicopper oxide	None	> 2,000 mg/kg bw
LD_{50}, dermal, rabbit (m/f)	Dicopper chloride trihydroxide		> 2,000 mg/kg bw
Dermal (EPA OPP 81-2) equivalent to OECD 402			
LD_{50}, dermal, rabbit	Dicopper oxide	Reddened skin, weight	> 2,000 mg/kg bw

(m/f)		gain, liver lesion	
LD_{50}, dermal, rabbit (m/f)	Dicopper chloride trihydroxide		> 2,000 mg/kg bw
Oral (EPA OPP 81-1)			
LD_{50}, oral, rat (m/f)	Dicopper chloride trihydroxide		1,200 mg/kg bw (m) 950 mg/kg bw (f)
Oral (OECD 423)			
LD_{50}, oral, rat (m)	Copper oxide		> 2,000 mg/kg bw
LD_{50}, oral, rat (m/f)	Coated copper flakes		300-500 mg/kg bw
Oral (OECD 401)			
LD_{50}, oral, mice (m/f)	Dicopper chloride trihydroxide		299 mg/kg bw
LD_{50}, oral, rat (m/f)	Copper sulphate pentahydrate		481 mg/kg bw
LD_{50}, oral, rat (m/f)	Copper sulphate pentahydrate	Lethargy, prostate posture, green coloured diarrhea, voiding few faeces and moribundity	482 mg/kg bw
LD_{50}, oral, rat (m/f)	Dicopper oxide	Piloerection, hunched posture, lethargy, decreased respiratory rate and diarrhea.	1,625 mg/kg bw (m) 928-2,000 mg/kg dw (f) 1,340 mg/kg bw (m/f)
LD_{50}, oral, rat (m/f)	Dicopper chloride trihydroxide		1,796 mg/kg bw (m) 2,006 mg/kg bw (f) 1,862 mg/kg bw (m/f)
LD_{50}, oral, rat (m/f)	Dicopper chloride trihydroxide		1,083 mg/kg bw (m) 1,854 mg/kg bw (f) 1,398 mg/kg bw (m/f)

Read across and bridging for acute oral toxicity

For copper massive and uncoated copper powder, the acute oral toxicity can be predicted using *in vitro* studies and available toxicity studies on other forms of copper and copper compounds. *In vivo* acute oral toxicity tests are available for several copper bearing materials. The results of the appropriate oral toxicity studies are summarised below. These include data on 2 substances, dicopper chloride and dicopper sulphide, which are not included in this OECD CoCam review programme.

- The acute oral effects - LD_{50} - observed for coated copper flakes are between 300 and 500 mg/kg.
- The acute oral effects - LD_{50} - observed for copper sulphate pentahydrate: 481 mg/kg.
- The acute oral lethal effects - LD_{50} - observed for copper chloride: 336 mg/kg.
- The acute oral lethal effects - LD_{50} - observed for copper oxide is >2000 mg/kg
- The acute oral lethal effects - LD_{50} - observed for dicopper sulphide is >2000 mg/kg

The acute oral data indicate the importance of bio-availability/bio-accessibility: *in vivo* exposure to highly bio-accessible copper compounds (coated copper flakes, copper sulphate pentahydrate and copper chloride) results in a higher acute toxicity than *in vivo* exposure to less bioaccessible/bioavailable copper oxide and dicopper sulphide. As read-across approach, the measured LD_{50} values of the all source materials (coated flakes, $CuS0_4.5H_2O$ and CuCl) were expressed as mg bio-accessible Cu/kg bw and combined with the % bio-accessible Cu released from the various copper bearing materials to predict the LD_{50} values. The results are given below.

Oral LD50 values for the various copper materials

Cu Material	**Copper content %**	**Bio-accessible/ bio-availability Cu %(1)**	**LD_{50} as bio-accessible Cu (mg Cu/kg bw) (2)**	**Measured LD_{50} LD_{50} (mg sub-stance/kg bw)**	**Calculated LD_{50} LD_{50} (mg sub-stance/kg bw) (3)**
Coated flakes (2.9m2/g)	99.7	57	227	**400 (mid value of 300 -500 mg/kg)**	215-401
$CuSO_4.5H_20$	25.4	25	122	**481**	480-894
CuCl	63.78	51	173	**336**	232-442
CuO*	80	15-76		**>2000**	160-1513
Cu_2S	78.9	2.7		**>2000**	4685-8718
Copper powder (0.024m2/g)	100	1.1			**11091-20636**
10 µm copper powder (0.067m2/g)	100	2.8			**4357-8107**

(1) Obtained from bioelution test or *in vivo* bioavailability test
(2) Measured LD_{50} / (1)
(3) Min-Max range (2) / (1)

The above Table shows comparable bioavailable/bioaccessible LD_{50} values for the 3 substances with bound LD_{50} data (122 to 227 mg bio-available mg Cu/kg bw). The calculated LD_{50} values for these materials (copper coated flakes, $CuSO_4.5H_20$ and CuCl) correspond to the measured hazard profile of these materials (LD_{50} < 2,000 mg/kg and > 200 mg/kg bw). Correct predictions are also observed for Cu_2S (i.e. LD_{50} > 2,000 mg/kg). For CuO, the predicted LD_{50} values are below the observed LD_{50} and therefore, calculations are conservative.
The data therefore support the concept that bio-available copper ions are responsible for the observed acute toxicity profiles of $CuSO_4.5H_20$, CuCl, Coated copper flakes CuO and Cu_2S and that *in vitro* bioaccessibility data can be used as read-across parameter.
Therefore, following the read-across approach, the *in vivo* toxicity of coated copper flakes and copper compounds were combined with the relative bio-accessibility of copper powders and massive to derive the classification of copper powders/massive. From the assessment it was concluded that copper powder (typical powder and worst case 10µm powder) and therefore also copper massive follow the same hazard profile as CuO and Cu_2S (LD_{50} > 2,000 mg/kg) : they do not merit acute oral classification.
Consideration of available acute oral toxicity data leads to the conclusion that coated copper flakes have the same hazard as the soluble copper compounds ($CuSO_4.5H_20$ and CuCl). CuO and Cu_2S and copper powder/massive do not present a hazard by the oral route.
Conclusion on the acute oral, dermal and inhalation routes

- Oral: the release of copper ions drive the acute oral toxicity. Dicopper oxide, copper sulphate pentahydrate, dicopper chloride hydroxide and coated copper flakes present a hazard by the oral route. Copper oxide, copper powder and copper massive are not hazardous by the oral route.

- Dermal: all tested substances within the category are not hazardous by the dermal route. Considering the lower solubility and bioaccessability of copper powders/massives compared to the tested copper

substances, copper powders/massive forms do not present a hazard by the dermal route.

- Inhalation: Dicopper oxide, dicopper chloride hydroxide and copper flakes are considered hazardous by the inhalation route. Copper sulphate pentahydrate, copper oxide and copper powder/massive are not hazardous by inhalation route

Skin, eye and respiratory irritation

Available key study data for irritation (skin, eye and respiratory tract):

Test substance	**Guideline**	**Result**	**Symptoms**
Dicopper oxide	OECD 404, rabbit	Not skin irritant	Very slight erythema and very slight oedema observed in the abraded skin
	OECD 405, rabbit	Eye irritant	Ocular irritation
	OECD 405, rabbit	Not eye irritant	/
	EPA OPP 81.4, rabbit	Not eye irritant	Conjunctival redness and chemosis
Copper oxide	OECD 404, rabbit	Not skin irritant	/
	OECD 405, rabbit	Not eye irritant	Scattered or diffuse corneal opacity, iridial inflammation
Dicopper chloride trihydroxide	OECD 404, rabbit	Not skin irritant	/
	EPA OPP 81.5, rabbit	Not skin irritant	/
	OECD 405, rabbit	Not eye irritant	Corneal effects
	EPA OPP 81.4, rabbit	Not eye irritant	Corneal and conjunctival effects
	OECD 405, rabbit	Not an eye iritant	Conjunctival effects
	OECD 405, rabbit	Not an eye irritant	/
Copper sulphate pentahydrate	OECD 404, rabbit	Not skin irritant	/
	OECD 405, rabbit	Severe eye irritant	Lesions
Coated copper flakes	OECD 404, rabbit	Not skin irritant	/
Coated copper flakes	OECD 405, rabbit	Slight eye irritation	corneal and conjunctival effects

Of the category substances, dicopper oxide, copper sulphate pentahydrate and coated copper flakes are considered an eye irritation hazard. Copper oxides and dicopper chloride hydroxide do not present a hazard for eye irritation. No data are available for copper powders.

None of the category substances are considered a skin irritation hazard.

Skin sensitization

Available key study data for skin sensitization:

Test substance	**Guideline**	**Result**	**Symptoms**
Dicopper oxide	OECD 406, guinea pig	Not sensitizing	No skin response after challenge.

Copper oxide	OECD 406, guinea pig	Not sensitizing	Mild skin response: 10% w/w: discrete or patchy erythrema at challenge sites in 4/10 animals) at 24h; no skin reaction at 48h. 5% w/w: discrete or patchy erythrema at challenge sites in 2/10 animals) at 24h; no skin reaction at 48h.
Dicopper chloride trihydroxide	OECD 406, guinea pig	Not sensitizing	No skin response after challenge.
	EU B.6, guinea pig	Not sensitizing	No skin response after challenge.
Copper sulphate pentahydrate	OECD 406, guinea pig	Not sensitizing	Slight erythema in 1/20 animals at 24h observation only.
Coated copper flakes	OECD 406, guinea pig	Not sensitizing	No skin response after challenge.

The available animal data suggest the chemicals are of low hazard

Repeated dose toxicity

Available key study data for repeated dose:

Test substance	**Toxicity**	**Method and study type details**	**Symptoms**	**NOAEL / LOAEL**
Copper sulphate pentahydrate	Oral	B.26 Rat m/f subchronic Dose: 0, 8, 17, 34, 67 or 138 mg Cu/kg bw/day, for 92 days for 7d/week, administrated in the feed	hyperplasia of the squamous, liver inflammation, altered clinical chemistry and urinary parameters, increased cytoplasmic droplets	NOAEL: 16.7 mgCu/kg bw/day
Copper sulphate pentahydrate	Oral	B.26 Mice m/f subchronic Dose: 0, 44, 97, 187, 398 and 815 mg Cu/kg bw/day in males, and 0, 52, 126, 267, 536 and 1058 mg Cu/kg bw/day in females for 92 days for 7d/week, administrated in the feed	hyperplasia of the squamous, liver inflammation, altered clinical chemistry and urinary parameters, increased cytoplasmic droplets	NOAEL: 97.2 mgCu/kg bw/day (m) 125.7 mgCu/kg bw/day (f)
Dicopper oxide (Cu^{2+})	Inhalation	OECD 412 Rat m/f 0.21, 0.41, 0.8, 2.0 mg/m^3 (analytical conc.) Vehicle: air Exposure: 28 days, 6 hours per	macrophages in the lung, increase in neutrophil number in BALF and blood, increase in LDH and protein levels in the BALF. Neutro-	NOAEC: >= 2 mg dicopper oxide/m^3 air

		day (5 days per week.)	phil-dominated inflammation in the lung. Most test substance-related effects at 2.0 mg/m^3 appeared to show a peak in the effect prior to completion of exposure. Decreased wet/dry lung weight ratio (highest exposure level only)	

Studies have shown that copper and copper compounds are considered equally or less bioavailable to a number of animal species when compared to copper sulphate, therefore the use of copper sulphate studies is justified on scientific grounds. The copper sulphate studies indicate that there is no evidence to indicate that copper or copper compounds present a hazard for repeat dose oral toxicity.

The inhalation study on dicopper oxide in the rat performed to a standard guideline is considered the most relevant. In this study, no serious adverse effects were observed up to the maximum test concentration (2 mg Cu/m^3 as dicopper oxide). Therefore dicopper oxide does not present a hazard for repeated dose inhalation toxicity.

Genotoxicity

Available key study data for genotoxicity:

Test substance	**Method and study type details**	**Test results**	**Evaluation of results**
Copper sulphate pentahydrate	OECD 471 *In vitro* Bacterial reverse mutation assay Salmonella typhimurium Doses: 1.6, 8, 40, 200, 1000 µg/plate (exp. 1) and 50, 100, 200, 400, 800 µg/plate (exp. 2)	Negative for Salmonella typhimurium Strains TA98, TA100, TA1535, TA1537, TA102 (all strains/cell types tested); metabolic activation: with and without; Cytotoxicity: yes	Negative
Copper sulphate pentahydrate	EU B.12 *In vivo* micronucleus assay mouse	Genotoxicity: negative	Negative
Copper sulphate pentahydrate	OECD 486 *In vivo* Oral: gavage unscheduled DNA synthesis rat	Genotoxicity: negative (m)	Negative

There is no human data available on the genotoxic potential of copper and copper compounds in humans. Copper and copper compounds are not genotoxic.

Carcinogenicity

Dietary copper/copper compounds have been administered orally to rats in long-term studies. None of the studies presented below meets exactly the requirements of the International Guidelines, but they do show conclusively that copper has no carcinogenic activity.

Two types of studies have been performed:

- Investigative toxicity studies demonstrating no tumor formation or long term effects even at very high dose levels.
- Co-administration with known carcinogens to demonstrate that copper is effective at reducing the incidence and delaying the onset of tumours.

Toxicity to reproductive organs and fertility and developmental toxicity

Available key study data for toxicity to reproductive organs and fertility:

Test substance	**Method and study type details**	**NOAEL**
Copper hydroxide	OECD 414 Teratogenicity Rabbit, f Oral: gavage Day 7-28 of gestation Dose: 0, 6, 9, 18 mg Cu/kg bw/day	Maternal toxicity reported at 9 mg/kg bw/d (inappetance and initial weight loss) and 18 mg/kg bw/d (deaths, weight loss). Effects on foetus (increased incidence of some common skeletal variants and 9 and 18 mg/kg d. NOAEL maternal toxicity 6 mg/kg bw/day NOAEL teratogenicity 6 mg/kg bw/day
Copper sulphate pentahydrate	OECD 416 Multi-generation Rat m/f 0, 100, 500, 1000, 1500 ppm in diet Two-generation study Exposure >= 70d before mating	1500 ppm or 23.6 mg Cu/kg bw/day (m) (P) 1000 ppm (F1 and F2) or 26.7 mg Cu/kg bw/day – reduced spleen weight (f)
Dicopper chloride	OECD 422 Rat m/f 0, 0.8, 3.2, 12.9, 51.7 mgCu/kg bw/day Reprotoxcity/developmental toxicity screening test	12.9 mg Cu/kg bw/day based on systemic and reprotoxic effects

In the teratogenicity study, maternal toxicity was represented by initial weight loss. These effects are considered to be local effects on the stomach in rabbits which result from gavage administration of copper hydroxide. Consequently, it is considered inappropriate to use data on maternal toxicity from this study as the basis of a repeat-dose NOAEL for copper. The spleen effect cannot be considered a reproductive effect. The existing toxicology data therefore supports the conclusion that copper has no reproductive or developmental toxicity potential.

The results of multi-generation study indicates that under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for reproductive toxicity was 1500 ppm (23.6 mg Cu/kg bw/day), the highest concentration tested. The NOAEL for P1 and F1 rats and F1 and F2 offspring during lactation was 1000 ppm, based on reduced spleen weight in P1 adult females, and F1 and F2 male and female weanlings at 1500 ppm however

the transient reduced spleen weights are not considered a reproductive endpoint as it did not affect growth or fertility.

Three of the substances and one form of zero valent copper in this category present a hazard for human health, based notably on the release/bioaccessibility of copper ions.

- **Copper sulphate pentahydrate: severe eye irritation and acute hazard by the oral route.**
- **Dicopper oxide: severe eye irritation, acute hazard by the oral and inhalation routes.**
- **Dicopper chloride hydroxide: acute hazard by the oral and inhalation route.**
- **Coated copper flakes: eye irritation, acute hazard by the oral and inhalation routes.**

Copper oxide, copper powder and copper massive do not pose a hazard to human health. In addition, the currently available evidence on the substances in the category do not cause concern for repeated dose toxicity, genotoxicity, reprotoxicity and carcinogenicity.

Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.
Note: A voluntary risk assessment of copper and copper compounds was performed in the context of the EU Existing Substances Regulation

Environment

Essentiality and copper background level

Copper is an essential micronutrient, needed for optimal growth and development of micro-organisms, plants, animals and humans. Copper deficiency and copper toxicity was experimentally observed in freshwater, marine water and soil organisms.

Considering that copper is a natural element, essential for all life forms, the safe upper threshold levels need to be compared with copper background levels, the optimal concentration ranges and essentiality levels. As an example, typical copper ambient background levels, reported for European surface waters, range between 0.1 and 14 µg Cu/L with an EU-wide median value of 0.9 µg Cu/L. Some studies demonstrated copper deficiency for freshwater organisms at levels ranging between < 1 and 10 µg dissolved Cu/L.

Environmental fate properties

Copper is a natural element and transition metal. The release of copper ions (eg Cu(II)) depends on the substance, particle size and characteristics of the receiving medium. The solubility of Cu_2O and CuO is dependent on pH. Data on solubility and/or transformation/dissolution (OECD 29) indicate that copper sulphate pentahydrate, dicopper chloride hydroxide and Cu_2O have higher solubility than CuO (Annex 1). Copper metal (Cu°) needs to be transformed to its ionic forms (Cu+/Cu2+) to dissolve copper-ions. Copper metal (Cu°) transformation/dissolution to ionic copper (Cu^{+}/Cu^{2+}) takes place at the surface of the copper particles and is related to the pH and surface area exposed.

Transformation/dissolution tests (OECD 29) on CuO and Cu°, demonstrate important pH dependent copper release rates of ionic copper. At pH 6, 7days transformation/dissolution of CuO releases more than 10 times more copper ions than at pH 7. Similarly, at pH 6, 7 days transformation/dissolution of Cu° releases 5 times more copper ions than at pH 7. The results from the transformation/dissolution tests of CuO, copper massive materials (spheres of 1-1.5 mm diameter), copper powders and coated copper flakes are summarised in the table below.

Transformation/dissolution of CuO and Cu° materials, in accordance to OECD 29

Material	pH	Mass load-	Surface loading	µg soluble Cu/L

		ing (mg/L)	(mm^2/L)	7 days	28 days
CuO	6	1		49	210
	7			5	9
	8			0	1
Copper massive - wire and epoxy mounted (1.5 mm)	6	100	43-47	6-19	
Copper massive (1 mm) - read-across from wire and epoxy-mounted	6	1	0.67	<1	
	6	10	6.7	1-3	
	6	100	67	9-27	
Copper massive (1 mm) (epoxy mounted)	6	1	0.67	1	3
Fine Copper powders (10-50µm) - read-across from wire and epoxy-mounted	6	1	67-107	9-44	37-176*
Coated copper flakes	6	1	2900	721	773
	7	1	2900	363	639

*From linear extrapolation of the7 days transformation/dissolution data

In conclusion, the information from solubility (see physico-chemistry) and transformation/dissolution tests with various copper-bearing materials demonstrate important differences in solubilisation properties ranging from fully soluble $CuSO_4.5H_2O$ to copper massive granules (1 mm diameter), with only 0.3% transformed/dissolved in 28 days at pH 6.
Hydrolysis, biodegradation and phototransformation are not applicable endpoints for copper and the inorganic copper salts.
The occurrence of various copper species will depend on the characteristics of the receiving environment. After being released into the environment, the Cu(II) ions typically bind to inorganic and organic ligands contained within water, soil and sediments. In water, Cu(II) binds to dissolved organic matter (e.g., humic or fulvic acids). The Cu(II) ion forms stable complexes with $-NH_2$, -SH, and, to a lesser extent, -OH groups in these organic acids. Cu(II) will also bind with varying affinities to inorganic and organic components in sediments and soils. For example, Cu(II) binds strongly to sulphides in sediments and to hydrous manganese and iron oxides in clay, and to humic acids, but much less strongly to aluminosilicates in sand. In all environmental compartments (water, sediment, soil), the binding affinities of Cu(II) with inorganic and organic matter is dependent on pH, the oxidation-reduction potential in the local environment, and the presence of competing metal ions and inorganic anions. The results of comparing the bio-availability of the Cu-ions in the receiving compartment must therefore be integrated in effects and risk characterisations.
Typical Kd-values for copper to freshwater suspended matter, freshwater sediment and soil are 30,246, 24,409 and 2,120 L/kg, respectively. Typical Kd-values for copper to marine and estuarine suspended matter are 131,826 and 56,234 L/kg, respectively. Typical Kd values correspond to 50^{th} percentiles of distribution of values from available monitoring data.

Scientific information on copper bioaccumulation factors (BCF, BAF, TTF) does not support the use of BAF or BCF values when they are used as traditional generic threshold criteria for the hazard potential since they are not an intrinsic property for copper. Therefore, for inorganic copper compounds, bioaccumulation factors should be used with caution (*Document ENV/JM/MONO(2001)*.

Indeed, for copper, acclimation and homeostatic regulation mechanisms are induced after longer exposure times. Furthermore, some organisms accumulate copper in a non-bioavailable form by using copper binding

and sequestrations mechanisms as regulation system. These adaptation and regulation systems play a role in the copper essentiality/toxicity profile and therefore, the BCF/BAF is not independent of exposure concentration and has no meaning for a hazard assessment.

Aquatic toxicity according to standard species/protocols

Different metal species are used as test substances in various ecotoxicity tests (e.g. $CuSO_4.5H_20$, $CuCl_2$, CuO). The metal ion (Cu^{2+}) drives the aquatic ecotoxicity and therefore, only tests with soluble inorganic copper compounds are retained. Acute and chronic toxicity data from the various soluble compounds (e.g. $CuSO_4.5H_20$, $CuCl_2$) were combined and expressed as soluble metal ion concentrations (µg dissolved Cu/L) causing a specific effect. To derive a reliable baseline data-set, the high quality measured toxicity values (µg dissolved Cu/L), obtained from the standard OECD test species and endpoints were retained.
High quality, acute $L(E)C_{50}$ values were retained from short term standard freshwater tests for 10 standard fish, invertebrate and algae test species (*Pseudokirchneriella subcapitata, Chlamydomonas reinhardtii, Chlorella vulgaris, Ceriodaphnia dubia, Daphnia magna, Oncorhynchus mykiss, Pimephales promelas, Lepomis macrochirus, Brachydanio rerio* and *Cyprinus carpio)*. Reliable values range between 3 and 9,150 µg Cu/L. The variability has been attributed to species-specific differences in sensitivity as well as water-characteristics such as pH, DOC and hardness. Species-specific geometric mean values range between 34 µg Cu/L (*Ceriodaphnia dubia*) and 2837 µg Cu/L (*Lepomis macrochirus*).

High quality, chronic NOEC(s) / EC_{10} values were retained from standard freshwater tests for 9 standard fish, invertebrate and aquatic plant test species (*Pseudokirchneriella subcapitata, Chlorella vulgaris, Chlamydomonas reinhardti* and *Lemna minor, Ceriodaphnia dubia, Daphnia magna, Oncorhynchus mykiss, Pimephales promelas* and *Salvelinus fontinalis*). Reliable values range between 2 and 337 µg Cu/L. The variability has been attributed to species and endpoint specific differences in sensitivity as well water-characteristics such as pH, DOC and hardness. Species-specific geometric mean values range between 12 µg Cu/L (*Ceriodaphnia dubia and Oncorhynchus mykiss*) and 137 µg Cu/L (*Chlorella vulgaris*). The information further indicates:

- The cellular mechanism of copper toxicity/deficiency, as well as the cellular mechanisms of copper homeostasis, has been largely preserved through evolution.
- The key indicator of copper toxicity is disturbance of the sodium homeostasis. The key target tissue for copper toxicity is therefore the water/organism interface, with cell wall and gill-like surfaces acting as target biotic ligands in all species investigated.
- The information on the ecotoxicity following exposures, through water and/or food and the information on metal bio-accumulation and homeostasis explain the observed small ratios between mortality and sub-lethal endpoints (typically a factor of 1 to 3).
- Large intra-species variability is observed and has been related to differences in copper species formed and different bio-availability in the various test media.

The hazard assessment of the substances in the category, derived from the acute $L(E)C_{50}$ or chronic NOEC(s) / EC_{10} values (µg dissolved Cu/L) and a molecular weight translation or the results from transformation/dissolution tests, shows that the copper compounds and the fine copper powders do pose a hazard to the environment. Coarse granules and massive copper materials release less copper ions and therefore pose less or no hazard to the environment under typical conditions.

Deriving the $HC_{5,50\%}$ from Species Sensitivity Distributions for freshwaters, marine waters and soils.

Several phenomena on the ecotoxicity of copper were considered for deriving $HC_{5,50\%}$ for freshwater, marine and soil compartments:

- The toxicity response is species-specific
- The toxicity response is dependent on the receiving environment
- The toxicity response is dependent on background levels

- The toxicity response is changing with time : e.g. ageing of copper in soils.

Freshwater

To derive a $HC_{5,50\%}$ value for the freshwater compartment, the standard chronic toxicity database was extended to include standard and non-standard species/protocols/endpoints**.** This resulted in a single-species chronic toxicity data–base of more than 200 NOEC/L(E)C_{10} values and 3 high quality, multi-species mesocosm studies. The observed single species NOEC/L(E)C_{10} values range between 2 and 510 µg Cu/L. The observed mesocosm NOEAECs[4] and LOEAEC [5] values were, respectively, 4 to 20 µg Cu/L and 9 to 40 µg Cu/L.

Accounting for species –specific differences : The copper aquatic effects database contains high quality, single-species chronic NOEC/L(E)C_{10} values for 27 species, representing algae, invertebrates (cladocerans, rotifer, molluscs, insects and amphipods), fish and higher plants. Species-specific geometric mean values range between 6 µg Cu/L (*Juga plicifera)*) and 137 µg Cu/L (*Chlorella vulgaris*). Considering the large number of species assessed, the statistical extrapolation method, applied to all NOEC/L(E)C_{10} values, is used to derive the $HC_{5,50\%}$.. Such Species Sensitivity Distribution was constructed using the non-normalised species-mean NOEC values for the most sensitive endpoints and resulted in a log normal $HC_{5,50\%}$ of 6 µg Cu/L.

Accounting for dependence on the water type: The species-specific NOECs observed are often characterised by large variability because Cu bioavailability and toxicity to aquatic organisms is influenced by abiotic parameters, such as pH, hardness and dissolved organic carbon (DOC). This raised the need to develop/use a bioavailability normalisation process for the $HC_{5,50\%}$ derivation. Chronic Biotic Ligand Models were developed for *Pseudokirchneriella subcapitata, Daphnia magna*, *Pimephales promelas* and *Oncorhynchus mykiss* in order to provide a mechanistic basis for understanding and predicting bioavailability through integration of chemical parameters (e.g. pH, hardness, DOC) and biological parameters (receptor sites on organism, mode of action).

The BLM models developed were further validated to represent the three basic trophic levels (algae, invertebrates and fish):
(1) a unified chronic model for the algae (*Pseudokirchneriella subcapitata, Chlamydomonas reinhardtii* and *Chlorella vulgaris*). The applicability of the model for predicting higher plant ecotoxicity (hydrocultures of barley) was demonstrated
(2) a chronic BLM for invertebrates (*Daphnia magna*). The capacity of the BLM for predicting copper toxicity to other invertebrates was demonstrated from copper toxicity studies with *Brachionus calyciflorus, Lampilis siliquoidea, Hyridella depressa* and *Hyalella azteca*
(3) a unified chronic model for 2 fish species (*Pimephales promelas and Oncorhynchus mykiss*).

The boundaries of the BLM applicability across species have been defined for pH (6-8.5), hardness (12-360 mg $CaCO_3$/L), dissolved organic carbon (DOC) (0-20 mg/L). The database showed under prediction for one field water with high Fe and Al and therefore boundaries were set as 332 µg dissolved Al/L and 332 µg dissolved Fe/L.

The BLMs developed for chronic fish (*P. promelas* and *O. mykiss*), invertebrates (*D. magna*) and algae (*P. subcapitata*) were used for normalising all retained chronic NOEC values of respectively fish, invertebrates and algae/plant species. Briefly, the bioavailability normalisation process normalises the NOEC/(L(E)C_{10} values to site-specific physicochemical conditions (i.e. pH, hardness and DOC).

The BLM normalised NOEC/(L(E)C_{10} values were used to construct Species Sensitivity Distributions for a range of physico-chemical conditions in European surface waters. Typical $HC_{5,50\%}$ s range between 7 and 30 µg Cu/L.

[4] NOEAEC : No Observed Ecological Adverse Effects Concentration
[5] LOEAEC : Lowest Observed Ecological Adverse Effects Concentration

Validation of the $HC_{5,50\%}$ derivation for multi-species systems: Species-specific NOECs and mesocosm specific NOEAECs / LOEAEC, protective of ecosystem structures and functions, are obtained from three distinct, high quality mesocosm studies, representing lentic and lotic system. Detailed comparisons between the BLM predicted and observed mesocosm effects, demonstrate that BLM could adequately predict the mesocosm sensitivity within a factor of 2.

Marine

The differences in physiology between freshwater and marine organisms, and the related differences in ecotoxic behaviour, led to the derivation of a separate $HC_{5,50\%}$ value for freshwater and marine environments. The estuarine compartment is not covered in this assessment.

The copper marine effects database contains more than 50 high quality, chronic NOECs/EC_{10}s values varying between 3 µg/L (*Phaeodactylum tricornutum*) and 145 µg/L (*Penaeus monodon*).

Accounting for species –specific differences: The copper marine effects database contains high quality, chronic NOECs/EC_{10}s values for 24 species. Species-specific geometric mean values range between 4 µg/*L (Phaeodactylum tricornutum*) and 145 µg/L (*Penaeus monodon*).

A Species Sensitivity Distribution was constructed using the species-specific NOECs and resulted in an $HC_{5,50\%}$ of 5 µg Cu/L.

Accounting for the characteristics of the marine water: Marine waters are characterised by high pH (typically around 8.3), high salinity (35‰) and high ionic strength. Unlike the inorganic composition of marine waters, DOC levels may vary considerable between marine water bodies. Open ocean waters usually have lower DOC, ranging between 0.5 and 1.8 mg/L. As for the freshwater system, Cu-availability and toxicity to marine organisms is therefore influenced by the strong binding of copper to the dissolved organic carbon (DOC). This raised the need to use an availability normalisation process.

A relationship between the EC_{50}s or NOEC/EC_{10}, values and the DOC levels were assessed for 6 species: *Fucus vesiculosus*, *Crassostreas gigas*, *Mytilus galloprovincialis*, *Dendraster excentricus*, *Strongylocentrotus purpuratu*s. Since the six data sets are statistically equivalent, these were combined for deriving an overall descriptor of the protective effects of DOC. This equation was used to translate all NOEC data to standard DOC levels of 2 mg DOC/L for coastal waters and 0.2 mg DOC/L for the open sea.

An organic carbon normalisation was carried out and the $HC_{5,50\%}$ was derived at a DOC levels representative of coastal and open ocean areas (2 and 0.2 mg/L). From the high quality data, $HC_{5,50\%}$ values of respectively 5.2 and 1.3 µg Cu/l, were derived.

Validation of the $HC_{5,50\%}$ derivation for a marine mesocosm: A marine mesocosm study resulted in NOEAEC and LOEAEC values of respectively 5.7 and 9.9 µg dissolved Cu/L. The mesocosm study therefore supports the $HC_{5,50\%}$ obtained from the single-species study. The assessment also confirmed that the DOC- normalised single species $HC_{5,50\%}$ is protective to the ecosystem structure and function.

Accounting for acclimation: copper deficiency is a well known phenomenon in open ocean but occurs at levels below the derived $HC_{5,50\%}$ for open oceans.

Terrestrial

The copper terrestrial effects database contains more than 250 high quality, chronic NOEC/EC_{10} values. The chronic NOECs/EC_{10}s vary between 8.4 mg/kg for *Eisenia andrei (*cocoon production) and 2,402 mg/kg (maize respiration). The lowest value is actually below the limit for essentiality for the species.

Information on 8 single species studies, in field contaminated soils, and 5 multi-species studies (freshly spiked and field contaminated) were used as an additional weight of evidence for the terrestrial compartment.

Accounting for species –specific differences: The copper terrestrial effects database contains high quality,

chronic NOEC values for 19 species and 9 microbial functions.

***Accounting for bioavailability dependence on the soil characteristics*:** To normalise the bio-availability data for soil type, a total of seven regression models were derived to predict toxicity of copper to terrestrial organisms for a wide range of soil types. For plants, the *L. esculentum* model (endpoint yield) was applied only on data for tomatoes, while all other plant data were normalised using the *H. vulgare* root elongation model because this endpoint is the most sensitive for plants. For invertebrates, the *E. fetida* model was used to normalise all soft-bodied species, while the *F. candida* model was used to normalise all hard-bodied species. For the microbial processes, all NOEC values related to the N-cycle were normalised based on the CEC slope of the nitrifying micro-organisms. The maize respiration model was used for normalisation of all microbial processes using a natural substrate. All other microbial processes were normalised using the substrate induced respiration model.

Accounting for soil leaching and ageing : Observed differences in toxicity of copper to terrestrial organisms, between lab spiked soils and field contaminated soils, allowed for the derivation of a leaching-ageing factor of 2, based on the 25-percentile of the ecotoxicity database. This factor was further supported by the mechanistic research on ageing and ionic strength (leaching) effects.

Deriving $HC_{5,50\%}$ values: Considering bio-availability and ageing, information from a large monitoring database allows calculating four $HC_{5,50\%}$ values of copper for soil samples taken from grazing land in European countries. The $HC_{5,50\%}$ values range between 13 and 205 mg Cu/kg dry weight, depending on the soil chemistry. A reasonable worst case 10th percentile of 69.6 mg Cu/kg dry weight is retained for the grazing land. A reasonable worst case 10^{th} percentile of 59.5 mg Cu/kg dry weight is retained for the arable land. The overall soil median reasonable worst case value across the two land-types is 64.6 mg Cu/kg dry weight.

Copper and copper compounds may present a hazard for the environment depending on the release/bioaccessibility of copper ions and on the conditions of the receiving environment (pH, hardness, presence and type of organic matter, anions and competing cations). Adequate screening-level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Note: A voluntary risk assessment of copper and copper compounds was performed in the context of the EU Existing Substances Regulation[6].

Exposure

Production and uses - copper - worldwide

The 2012 global production of copper was 25.7 million tonnes. Approximately 20.2 million tonnes was produced from mining (primary production) and the smelting/refining of complex, end of life materials (secondary production). Another 5.5 million tonnes, combing offcuts from the value chain and clean, end-of- life scrap, were recycled directly by the producers of semi-fabricated products.

Recognising the locations of today's copper mines, Latin American is the main exporting region. The major importers are Asia, (particularly China, India and Korea) and, to a lesser extent, Europe. North America is

[6] *http://echa.europa.eu/copper-voluntary-risk-assessment-reports*

reasonably balanced between production and demand.

Production and uses - copper – Europe

EU production volume in 2012 of copper has stabilised at around 1.5 million tonnes for smelting and 1.8 million tonnes for refining. Additionally, around 1.3 million tonnes of scrap (secondary recycled raw material) is used as feedstock material. Besides the production, about 0.6 million tonnes of refined copper are imported in the EU.

Copper massive forms account for +/- 99.6% of the market. Principal uses include copper wire, for power cables, building wire, electric motors and voltage transformers, copper tubes and fittings, for domestic water, gas distribution, water heating systems and air conditioning, strip for the electronics industry and sheets for roofing, gutters and down-pipes.

Extrapolating EU data, copper powders are estimated to account for +/- 0.4%. They are mainly used for friction materials such as for vehicle brake pads, carbon brushes for electrical motors and sintered parts for engineering components.
Coated copper flakes represent less than 0.1% and are used mainly as pigments and as an active ingredient in antifouling paints.

Copper oxide is used as wood preservative (biocidal/antimicrobial), catalyst, brake pads, industrial (glass, ceramics).
Dicopper oxide is used as antifouling (biocidal/antimicrobial), fungicide (agrochemical), catalyst, "hot" industrial processes.
Copper sulphate pentahydrate is used as algaecide (biocidal/antimicrobial), fertiliser, raw material use, general industrial uses (dyes, mineral flotation, ceramics, glass), animal feed and foodstuffs.
Dicopper chloride hydroxide is used as fungicide (agrochemical), fertiliser and industrial uses e.g. ceramics

EU- exposure

Sources

Copper is a naturally occurring element that can be found at background levels in water, sediment and soil. Total copper releases were dominated by agricultural uses (feed additives and fertilizers, 39%) and traffic (mainly brake pads, 43%). Massive copper uses (wear of overhead wires, corrosion of copper tubes, fittings and taps and external building applications (roofs, gutters, down pipes, facades)) contribute to 15% of the total anthropogenic EU emissions. The relative contribution from waste incineration plants and landfill facilities is minor (0.4%). Other minor copper releases, that have been observed include, among others, industry releases, domestic and industrial heating, fireworks and domestic wastewaters .

Monitoring

Background levels of copper in water, sediment and soil are reported in the EU FOREGS Geochemical Atlas (Forum of European Geological Surveys). Median natural background concentration levels in Europe are 0.88 µg dissolved Cu/L for surface water (rivers and lakes), 14 mg/kg dry weight for river and lake sediment and 12 mg/kg dry weight for topsoil. Region-specific dissolved Cu freshwater PEC values, derived for Austria, Belgium, Denmark, Finland Barentz area, Germany Elbe, Ireland, Portugal, The Netherlands, Sweden, England, Wales and Scotland ranged between 0.5 and 4.7 µg dissolved Cu/L with a median of 2.7 µg dissolved Cu/L. Measured PECs for the EU-15 are 67,5 mg/kg dw for sediment and 31 mg/kg dw for agricultural soil.

Humans exposed via the environment

The contribution to dietary intake (copper from anthropogenic origin in fruit and vegetables, locally grown, and other foodstuffs) in the local environment was rather low due to the impact of industrial air pollution control measures and the effective homeostatic control of copper uptake by plants. External exposure through inhalation is even more limited.

Occupational exposure

The sectors that have been identified for estimating local exposures include: Smelting and Refining, Wirerod & Cables production, Casting Billets and Plates, Production of semi-finished copper shapes, Production of Copper Powders and Copper Chemicals. For melting and casting of billets and further processing, respirable copper as a function of total copper ranges from 6-25% with a median value of 9%. For smelting a single value of 13% is given while for non-foundry operations in the manufacture of copper powders the single value of 4%.

Consumer exposure

Consumer exposure to copper may occur via dermal or oral routes or via inhalation. Dermal exposure occurs mainly through the use of toiletries and cosmetics face cream and hair care products, through coin handling or jewellery. Additional dermal exposure is possible from the use of special paints or from copper containing wood preservatives and pesticides. Oral exposure (other than from food and water) occurs in particular by ingestion of dietary supplements containing copper, inhalation exposure occurs mainly through cigarette smoke. Internal exposure may also occur with the use of intra-uterine devices. There are no known exposures of consumers to other copper compounds covered in this category.

Limitations

The hazard profile is based on intensive literature searches and targeted research programs carried out for the European hazard classification and risk assessment regulation during the period 2000-2006. Recent findings are not included.

ANNEX 1: Standard OECD Solubility of copper compounds

Compound	pH range			
	5.5-6.5	**>6.5-7.5**	**>7.5-8.5**	**>8.5-10**
	Solubility (mg/L)			
$CuSO_4.5H_2O$	220000			
$Cu_2Cl(OH)_3$	1.19	-	-	0.525
Cu_2O	-	0.639	-	0.539
CuO	0.394	-	-	0.01