Workplace Exposure Standard (WES) review

COPPER
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New Zealand Government

WORKSAFE
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appendices

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for copper should be changed.

It considers the potential for exposure to copper in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposure.

The review includes a recommendation to change the WorkSafe WES for copper, which is currently set at a **WES-TWA** of 0.2**mg/m³**, for **inhalable fraction** of copper **fume** and a WES-TWA of 1mg/m³, for inhalable fraction of copper dusts and mists, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: **Cu**; Copper powder; Pigment metal 2; Bronze powder.

2.0 Chemical and physical properties

Copper is a reddish, lustrous, malleable, odourless, metallic solid at room temperature (**NLM** PubChem, 2019).

Chemical and physical properties of copper include:

Molecular weight	63.55g/mol
Formula	Cu
Specific gravity	8.92g/cm^3
Melting point	1083°C
Boiling point	2567°C
Volatility	Non-volatile at 20°C
Solubility	Insoluble in water; Soluble in nitric acid and hot sulphuric acid

NLM PubChem, 2019; **DFG**, 2017; **SCOEL**, 2014; **ACGIH**®, 2001.

TABLE 1: Physicochemical properties of copper

Health-related hazard classifications for 4,6-dinitro-*o*-cresol:

	HSNO CLASSIFICATION
Substance	Copper, powder
CAS No.	7758-97-6
Classification	6.1B (All); 6.1B (O); 6.1B (I); 6.4A; 6.5B; 6.6A; 6.9B (All); 6.9B (O); 6.9B (I)

TABLE 2: **HSNO** hazard classifications of copper (**EPA**, 2019)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.

[O] Oral exposure route.

[D] Dermal exposure route.

[I] Inhalation exposure route.

3.0
Uses

Copper is used extensively where high electrical and thermal conductivity are required (ACGIH®, 2001).

Copper products include copper wire, copper tubing and fitting systems, and building construction materials. Copper powders are used in sintered parts for engineering components and filters; carbon brushes for electrical motors; and friction materials (**EU vRAR**, 2008).

Copper compounds are used in fungicides, ceramics, and pyrotechnics; as pigments and analytical reagents; and, for electroplating and many other industrial uses. Copper fume exposures can occur in copper and brass foundries and smelters, and in welding copper-containing metals (ACGIH®, 2001).

Occupational exposure to copper can occur during production, storage, transportation and end-use.

Workers can be exposed to copper via inhalation and eye or dermal contact.

The number of workers exposed or potentially exposed to copper in New Zealand workplaces is unknown.

Statistics New Zealand 2018 data indicate that 51,570 New Zealand workers were working in the areas of:

- other agriculture and fishing support services
- pesticide manufacturing
- copper, silver, lead and zinc smelting and refining
- non-ferrous metal casting
- metal roof and guttering manufacturing (except aluminium)
- machinery and equipment manufacturing (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

Copper is an essential element, which is incorporated in various proteins and its toxicokinetics are regulated by homeostasis (SCOEL, 2014; EU vRAR, 2007). It is a constituent of more than 20 enzymes (SCOEL, 2014).

4.1 Non-cancer

Humans

The SCOEL recommendation on copper and its inorganic compounds noted the acute toxicity potential in exposed humans:

> "The inhalation of copper fumes (copper oxide) or fine copper dusts was associated with 'metal fume fever' with a burning sensation, redness of the throat, coughing, sneezing, shortness of breath, nausea, rigor and fever. These effects occurred usually within a few hours after exposure and lasted for 24–48 hours (**ATSDR** 2004, Greim 2006). Quantitative data on exposure concentrations were scarce. A recent analysis of seven published studies with reports of copper-induced metal fume fever could not find clear evidence that copper was indeed the causative agent (because of lack of valid exposure assessment, atypical symptoms and lack of consistency among the types of work associated with the effects) (Borak et al 2000). In a cross-sectional study by Jayawardana (2004) on brass workers, the occurrence of acute symptoms of metal fume fever was also mentioned, but the workers were also exposed to zinc (exposure concentrations not stated). Zinc oxide is a well-known inducer of metal fume fever. According to unpublished data from the copper welding and refining industry, concentrations up to 0.4**mg** Cu/m³ resulted in no ill effects (ACGIH® 2001). Because no further details are given, these data are not suitable to derive a no observed adverse effect concentration (**NOAEC**)."
>
> "There are several case reports of single oral exposures to copper compounds accidents, suicide attempts, uptake of contaminated beverages. The observed symptoms included metallic taste, epigastric burning, nausea, abdominal pain, vomiting and, in more severe cases, lethargy, haemolytic anaemia, damage of liver and kidney as well as sometimes coma and death (ATSDR 2004, **WHO** 1998). Several controlled studies with human exposure to a single oral dose of copper sulphate in drinking water after an overnight fast revealed a lowest observed adverse effect level (**LOAEL**) for first gastrointestinal effects (nausea) of 0.011–0.017**mg Cu/kg bw** and a no observed adverse effect level (**NOAEL**) of 0.0057–0.011mg Cu/kg bw (Araya et al 2001 and 2003a, Olivares et al 2001, all cited in ATSDR 2004)." (References cited in SCOEL, 2014).

The New Zealand EPA classifies copper as a 6.1B substance – a substance that is acutely toxic (EPA, 2019).

The SCOEL recommendation on copper and its inorganic compounds summarised the irritation/corrosion potential in exposed humans:

> "Occupational exposure to 111–464mg/m³ metallic copper dust caused symptoms of irritations of the respiratory tract (Suciu et al 1981). Irritation of the respiratory tract and the eyes were noted in other studies with occupational exposure to copper dust or oxide, but exposure concentrations were not determined (Askergren and Mellgren 1975, Jayawardana 2004). Finelli et al (1981) stated the occurrence of conjunctivitis in workers exposed to copper dust concentrations of 0.64–1.05mg/m³ (co-exposure with iron, lead and cadmium). In the study by Gleason (1968), no irritation of the lower respiratory tract was reported (exposure to 0.12–0.36mg Cu/m³ as copper dust).

> "Dermal contact with copper salts may cause irritation to the skin, itching and erythema. Contact of copper salts with the eye may lead to conjunctivitis, ulceration, turbidity of the cornea and adhesion of the eyelids to the eye (no further details) (WHO 2002)." (References cited in SCOEL, 2014).

The New Zealand EPA classifies copper as a 6.4A substance – a substance that is irritating to the eye (EPA, 2019).

The SCOEL recommendation on copper and its inorganic compounds summarised the sensitisation potential in exposed humans:

> "Copper and copper sulphate may evoke allergic contact dermatitis. Testing of patients with contact eczema or of workers occupationally exposed to copper dust or fumes provoked dermal reactions following testing with copper sulphate in concentrations up to 5%. However, the number of reported cases with a clear copper-induced sensitisation is very low and has been observed only at high concentrations of 5% of copper salts (Walton et al 1983a,b, both cited in Greim 2006). The observed dermal reactions were mostly either unspecific or cross reactions to a nickel allergy. In some cases, they may have been provoked by nickel contaminations of the copper (Greim 2006).
>
> "A single case of occupational respiratory sensitisation is reported. A worker in the galvanic industry showed a 30% decline of the forced expiratory volume in the first second (**FEV1**) after 4 hours after provocation with 1mg copper sulphate/m^3 (Cirla 1985)." (References cited in SCOEL, 2014).

The New Zealand EPA classifies copper as a 6.5B substance – a substance that is a contact sensitiser (EPA, 2019).

The SCOEL recommendation on copper and its inorganic compounds summarised the repeated dose toxicity in exposed humans:

> "Gleason (1968) reported symptoms similar to metal fume fever (Section 3.2) in an unknown number of workers after occupational exposure to copper dust during polishing of copper plates with aluminium oxide abrasive. The effects (general feeling of discomfort, slight sensations of chills and warmth, stuffiness of the head) were first reported some weeks after the start of exposure. Measured exposure was 0.12mg Cu/m^3 but, according to the author, the workers may sometimes have been exposed to 2- to 3-fold higher concentrations. The effects did not disappear until an exhaust system was installed, which reduced exposure to 0.008mg Cu/m^3.
>
> "Suciu et al (1981) examined about 100 workers chronically exposed to 111–464mg Cu/m^3 as copper dust. At the higher concentration levels, the authors reported an increased incidence in respiratory effects, gastrointestinal complaints, neurotoxic symptoms, cardiovascular and peripheral vascular disorders, hepatomegaly and impotence. No control group was included in this study. Finelli et al (1981) observed mild anaemia, hepatomegaly and bronchitis in workers who were exposed to copper dust concentrations of 0.64–1.05mg/m^3. These workers were also exposed to iron, lead and cadmium. A more recent cross-sectional study by Jayawardana (2004) of brass workers reported anorexia, distaste, aches and pain after chronic occupational exposure (exposure concentration not stated, co-exposure with zinc)." (References cited in SCOEL, 2014).

The New Zealand EPA classifies copper as a 6.9B substance – a substance that is harmful to human target organs or systems (EPA, 2019).

The DFG **MAK** Value Documentation on copper and its inorganic compounds noted:

> "... the study by Gleason (1968), even if insufficiently documented, does indicate that the NOAEC (no observed adverse effect concentration) for the inhalation of very fine metallic copper at the workplace is about 0.008mg copper/m^3, whereas influenza-like symptoms occur at concentrations in the range from 0.12 to 0.36mg/m^3." (Reference cited in DFG, 2015).

The EU vRAR on copper and specified copper compounds noted:

> "Several studies are available which have investigated the effects of repeated inhalation exposure to copper in humans. In all cases, qualitative and quantitative data on exposure are absent." (EU vRAR, 2007).

The EU vRAR on copper and specified copper compounds summarised the reproductive/developmental toxicity in exposed humans:

> "The available data concerning reproductive effects of copper in humans are sparse. Of the four human studies which have been reviewed here, two have major deficiencies which make the reliability of their findings uncertain. The remaining two studies, both drinking water studies, failed to demonstrate any association between copper levels in drinking water and adverse pregnancy outcome." (EU vRAR, 2007).

The SCOEL recommendation on copper and its inorganic compounds noted that no human data on genotoxic potential was available (SCOEL, 2014).

The New Zealand EPA has not classified copper as a 6.6A substance – a substance that is a known or presumed mutagen (EPA, 2019).

Animals

The DFG MAK Value Documentation on copper and its inorganic compounds summarised the acute toxicity potential in experimental animals:

> "In rabbits, the **LC_{50}** for copper(II) hydroxide was >1303mg/m^3 copper (no further details) (WHO 1998).
>
> "A 1-hour exposure of guinea pigs to an aerosol of copper(II) oxide (copper concentration 1.3mg/m^3, particle diameter 0.03**µm**) led to a significant decrease in the tidal volume, the respiratory volume per minute, and pulmonary capacity during and after the exposure (Chen et al. 1991).
>
> "One hour after a 4-hour inhalation exposure of Syrian golden hamsters (6 to 12 animals per group) to an aerosol of copper(II) sulfate pentahydrate (0.5, 4.8, 6.1, 8.7 or 10.8mg/m^3, corresponding to copper concentrations of 0.13, 1.2, 1.5, 2.2 or 2.7mg/m^3), the uptake of instilled radioactive colloidal gold into lung macrophages was dose-dependently reduced at copper concentrations of 1.2mg/m^3 and above, which was reversible within 48 hours. The volume of the macrophages was significantly decreased. The **EC_{50}** value for copper was 1.8mg/m^3 (Skornik and Brain 1983)." (References cited in DFG, 2006).
>
> "After dermal exposure of rats to copper(II) oxysulfate or of rabbits to copper(II) hydroxide, the **LD_{50}** values reported for copper were >1124 and >2058**mg/kg** body weight per day, respectively (WHO 1998)."

> "The acute lung toxicity after single intratracheal instillation of copper(II) sulfate pentahydrate (purity 99.9 %) or copper(II) oxide (purity >99.9 %) was investigated in adult Wistar rats. Within 12 hours and up to 3 days after instillation, there was an increase in the number of alveolar macrophages and a significantly increased activity of lactate dehydrogenase and ß-glucuronidase in the bronchoalveolar lavage fluid after copper doses of 0.018mg/kg body weight and above for the soluble salt, and copper doses of 0.073mg/kg body weight and above for the insoluble oxide. The inflammation potential was similar for both compounds (Hirano et al. 1990, 1993). The lethal dose for copper(II) oxide after intratracheal instillation was 222mg/kg body weight in rats (WHO 1998)." (References cited in DFG, 2006).

The SCOEL recommendation on copper and its inorganic compounds summarised the irritation/corrosion potential in experimental animals:

> "Dermal contact with copper salts may cause irritation to the skin, itching and erythema (no further details) (WHO 2002).
>
> "Dermal application of metallic copper caused follicular reactions in guinea pigs (Greim 2006). Necroses were observed after dermal exposure of mice to copper chloride in dimethyl sulphoxide (**DMSO**) at concentrations ≥2.5% (Basketter et al 1999)."
>
> "Contact of copper salts with the eye may lead to conjunctivitis, ulceration, turbidity of the cornea and adhesion of the eyelids to the eye (no further details) (WHO 2002)." (References cited in SCOEL, 2014).

The SCOEL recommendation on copper and its inorganic compounds summarised the sensitisation potential in experimental animals:

> "Two maximisation tests in guinea pigs with the pentahydrate of copper sulphate in petrolatum yielded conflicting results (Boman et al 1979, Karlberg et al 1983, both cited in Greim 2006). As these studies were done by the same working group at similar conditions, the reason for this discrepancy is unknown. One Local Lymph Node Assay (**LLNA**) in mice with 10% copper sulphate pentahydrate in ethanol failed to show a positive reaction (Ikarashi et al 1992). Another LLNA with copper chloride (1–5% in DMSO) exhibited a strong lymphocytic proliferation, but this was attributed to the local necrotic action of the compound (Basketter et al 1999)." (References cited in SCOEL, 2014).

The DFG MAK Value Documentation on copper and its inorganic compounds noted:

> "In a maximization test in 5 female Hartley guinea pigs, copper naphthenate was tested for its contact sensitizing effects and its cross-reactivity to copper(II) chloride. The animals were given 1% or 25% copper naphthenate (vehicle not specified) for intradermal and epicutaneous induction, and 0.5% of the test substance in petroleum ether as the challenge treatment. The reason for selecting a challenge concentration that was lower than the topical induction concentration by a factor of 50 was not explained. The skin reactions were evaluated according to the degree of erythema (score 0–4) and oedema (score 0–3). The mean reaction score (**MR**) for all the animals treated in the different groups, was calculated from the sum of the reaction scores. No reaction to copper naphthenate or 1% copper(II) chloride (in ethanol) could be induced (MR = 0) after pretreatment with copper naphthenate in any of the 5 treated animals or in any of the 5 control animals (Yamano et al. 2006).

> "The substance was additionally tested in a local lymph node assay (LLNA) in BALB/c mice. According to the results, copper naphthenate preparations in petroleum ether/olive oil (4:1) were not sensitizing (stimulation index (**SI**) <2) up to concentrations of 1%. The findings with higher copper naphthenate concentrations (irritation measured as the increase in ear thickness), are suggestive of a primary irritating effect (3%: SI approximately 6, slight irritation; 10%: SI approximately 9, marked irritation) (Yamano et al. 2006)." (References cited in DFG, 2015).

The EU vRAR on copper and specified copper compounds summarised the repeated dose toxicity in experimental animals:

> "Two studies are available which have investigated the effects of repeated inhalation exposure to copper-containing aerosols. However, both studies deviate from Annex V requirements in several important aspects and there are uncertainties regarding the reliability and/or biological significance of their findings. Consequently, these studies provide limited information concerning the effects of repeated inhalation exposure and any dose-response relationship which are relevant to human risk assessment, and provide no data which can be carried forward to 'Risk Characterisation'."
>
> "No data are available on the effects of repeated dermal exposure to copper substances in animals." (References cited in EU vRAR, 2007).

The EU vRAR on copper and specified copper compounds summarised the reproductive/developmental toxicity in experimental animals:

> "Results of a two-generation reproduction toxicity test in rats, conducted in accordance with Annex V and **OECD** guidelines, showed no treatment-related effects on reproductive parameters in either the parental generation or offspring associated with a diet containing copper sulphate. The NOAEL for reproductive toxicity in this study was 1500**ppm** dietary copper sulphate pentahydrate (equivalent to 381ppm copper), the highest concentration tested.
>
> "It is noted that the NOAEL of 250ppm Cu for reduced spleen weight is consistent with the NOAEL for repeated dose toxicity reported by Hébert et al (1993) ..."
>
> "Additional useful data on fertility have been provided by a repeated exposure dietary study (Hébert 1993). This study showed that consumption of copper, as copper sulphate, at up to and including 68**mg Cu/kgBW/day** in rats and 536mg Cu/kgBW/day in mice for 13 weeks had no effect on male reproductive organ weights, spermatid or spematozoal measurements, oestrous cycle length or proportion of oestrous cycle spent in each stage. Effects on other reproductive parameters were not examined in this study.
>
> "Several animal studies have been published which have investigated developmental toxicity of copper compounds. Only one of these studies, conducted by Munley (2003a), conforms to recommended test methods (Annex V Test Guideline B.31; OECD Tets Guideline 414) and currently this provides the most reliable data on the developmental toxicity of copper. The findings of this study showed that developmental effects in rabbits, namely increased occurrence of a common skeletal abnormality, were only apparent at doses of copper hydroxide which caused maternal toxicity as indicated by initial weight loss and inappetance. There were no indications of fetal abnormalities associated with treatment at up to maternally toxic levels. The NOAEL for maternal toxicity and developmental effects in rabbits in this test was 6mg Cu/kgBW/day. Effects on the fetus were considered to

be secondary to maternal toxicity and thus not a specific effect of copper on reproduction. Maternal toxicity in this study was considered to be a local effect on the stomach resulting from gavage administration and consequently provides no basis for deriving a NOAEL for repeat-dosing toxicity.

"Other studies investigating developmental effects in animals have significant deficiencies in methodology and/or reporting. In some of the studies which showed developmental effects, there was clear evidence of maternal toxicity; in other studies, maternal toxicity could not be ruled out. Consequently, these studies provide little useful information concerning the developmental effects of copper compounds which are relevant to human risk assessment.

"Investigations of the effects of copper-containing IUDs on foetal development and other reproductive parameters in animals have failed to demonstrate any effects which could be associated with exposure to copper." (References cited in EU vRAR, 2007).

The SCOEL recommendation on copper and its inorganic compounds summarised the genotoxic potential in *in vitro* test systems and experimental animals:

"Copper compounds were not mutagenic in most studies in bacteria and yeasts. Copper sulphate and chloride produced no mutations in *Salmonella* strains TA98, TA100, TA102, TA1535 and TA1537 with or without metabolic activation, even at cytotoxic concentrations or at the limit of solubility. A lack of response was also reported up to cytotoxic concentrations without metabolic activation in the **SOS** Chromotest (*Escherichia coli* PQ37), in *E. coli* WP2, in rec assays with *Bacillus subtilis* (H17 and M45), in a test for streptomycin independence in *E. coli* Sd4-73 and in tests for penicillin or streptomycin resistance in *Micrococcus aureus* FDA209 (ATSDR 2004, Greim 2006, WHO 1998).

"Copper nitrate induced dose-dependent gene mutations, sister chromatid exchange and **DNA** strand breaks in V79 hamster cells (0.01–0.5**mmol/l**, without metabolic activation) (Sideris et al 1988, cited in Greim 2006 and WHO 1998). DNA single strand breaks in rat hepatocytes were reported after exposure to copper sulphate, but only at a cytotoxic concentration of 1mmol/l (Sina et al 1983, cited in Greim 2006). Copper sulphate induced a roughly dose-dependent increase in unscheduled DNA synthesis and an accumulation of copper in the nucleus of rat hepatocytes in the range of 7.9–78.5**µmol/l** (Denizeau and Marion 1989). In Chinese hamster ovary (**CHO**) cells, and to a lesser extent also in human fibroblasts, DNA-protein crosslinks were induced following exposure to copper sulphate at 1–2mmol/l, but not at 0.5mmol/l (Olin et al 1996, cited in Greim 2006). In HeLa cells, copper sulphate interfered with the repair of oxidative DNA damage and inhibited poly(**ADP**-ribosyl)ation at concentrations starting from 100µmol/l, while in the same study the induction of DNA strand breaks and oxidative DNA base modifications was restricted to cytotoxic concentrations of 300µmol/l and higher (Schwerdtle et al 2007). Cu(II) chloride induced minimal DNA double-strand breaks (single cell electrophoresis assay at neutral pH) in human **CD4+** T cells at 0.5**mM**, but no viable cells were found in the subsequent higher concentrations (Caicedo et al 2008). DNA strand breaks were also observed with Cu(II) chloride in peripheral mouse blood lymphocytes at 10µM (Urbina-Cano et al 2006) without data on cytotoxicity.

"Karlsson et al (2008, 2009) showed that CuO nanoparticles were highly potent regarding cytotoxicity, mitochondrial damage, the induction of reactive oxygen species, DNA strand breaks and oxidative DNA base modifications (comet assay) when the human lung epithelial cell line A549 was exposed to the particles.

"Another study showed also a strong induction of genotoxic response towards CuO nanoparticles in human pulmonary epithelial cells (A549) by activating the **p53** pathway and up-regulation of the DNA damage repair proteins **Rad51** and **MSH2** (Ahamed et al 2010)."

"Single intraperitoneal injection of copper sulphate pentahydrate to Albino mice induced a significant and dose-related increase in chromosomal aberrations (chromatid type) at doses of 1.1–6.6mg Cu/kg bw. There was also an increase of chromosomal breaks at the highest dose (Agarwal et al 1990, cited in Greim 2006 and WHO 1998).

"A study by Bhunya and Pati (1987, cited in Greim 2006 and WHO 1998) reported an increase in chromosomal aberrations (chromatide gaps) in Swiss mice, which were intraperitoneally injected in single doses of 1.3–5mg Cu/kg bw as copper sulphate, either given as a single dose or in 5 daily doses. Further studies were carried out with single doses of 5.1mg Cu/kg bw by the oral or subcutaneous route. All exposures resulted in significant increases in chromosomal aberrations. In the mice dosed once intraperitoneally, the effect was dose-dependent. In parallel studies with the same strain of mice, these authors also reported a significant and dose-dependent increase in the incidence of micronuclei after two intraperitoneal injections (24 hours apart) of doses of 1.3–5mg Cu/kg bw and day as copper sulphate. The authors used no positive controls and there were signs of cytotoxic effects at all doses.

"A significant and dose-dependently increased rate of micronuclei was also reported in a study by Rusov et al (1997, cited in Greim 2006). These authors exposed BALB/c mice twice intraperitoneally at 14-hour intervals to copper acetate at doses of 0.3–13.0mg Cu/kg bw. Male and female CF1 mice were gavaged for 6 consecutive days with $CuSO_4$ (8.25mg Cu/kg bw and day). This dose regimen induced micronuclei in bone marrow cells and was genotoxic when evaluated in the neutral and the alkaline version of the comet assay in whole blood (Prá et al 2008). Data on cytotoxic effects on bone marrow were not given. Saleha et al (2004) also detected DNA single-strand breaks by the comet assay in leukocytes from male Swiss albino mice administered orally up to 4.9mg Cu/kg bw as copper sulphate. The trypan blue exclusion technique showed a cell viability ranging from 90–95%. DNA single-strand breaks, detected by the comet assay (Franke et al 2006), were also induced in blood cells from male and female Swiss Webster mice after oral administration of copper sulphate (8.50Cu **mg/kg bw**). In contrast to these findings, Tinwell and Ashby (1990, cited in Greim 2006 and WHO 1998) did not observe an increase in micronuclei following a single intraperitoneal injection of copper sulphate pentahydrate at doses of 1.7–5.1mg Cu/kg bw to CBA mice." (References cited in SCOEL, 2014).

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] has no evaluation on the carcinogenic potential of copper. (IARC, 2019).

The US National Toxicology Program [NTP] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of copper (NTP RoC, 2019).

The NZ EPA has not classified copper as a 6.7A or 6.7B substance – substances that are known or presumed, or suspected human carcinogens respectively (EPA, 2019)

Humans

The SCOEL recommendation on copper and its inorganic compounds summarised carcinogenicity data in exposed humans:

> "Epidemiological studies reported increased incidences for the overall cancer mortality as well as mortality due to lung and stomach cancer in workers exposed to copper, especially in copper smelting processes (copper oxide). Due to the lack of exposure characterisation and the possible influence of confounding factors (smoking, co-exposure to arsenic and elevated individual copper serum levels in consequence of several diseases including cancer) these studies are not adequate to derive a causal relationship between inhalation exposure to copper compounds and cancer (ATSDR 2004, Greim 2006). Suciu et al (1981) reported the occurrence of 7 pituitary adenomas in workers who were exposed to 111–464mg Cu/m^3 as copper dust. Due to the insufficient diagnosis and description of these tumours, it is not possible to draw a firm conclusion regarding the carcinogenic potency of copper dust (Greim 2006). There are no qualified studies on the carcinogenic action of copper in humans via the oral route (ATSDR 2004, WHO 1998)." (References cited in SCOEL, 2014).

Animals

The EU vRAR on copper and specified copper compounds summarised carcinogenicity data in experimental animals:

> "Several animal carcinogenicity studies have been conducted with copper compounds. Short duration, low level of exposure, inappropriate exposure route, small sample sizes and/or limited histopathologic examination limit the findings of these studies. Nevertheless, these studies provide no indication that copper compounds are carcinogenic." (EU vRAR, 2007).

4.3 Absorption, distribution, metabolism and excretion

The SCOEL recommendation on copper and its inorganic compounds summarised the **ADME** in humans:

> "No quantitative data exist for the rate of absorption by the inhalation route and copper absorption will depend on the chemical characteristics of the actual compound. An oral daily uptake of 1–3mg/day is considered necessary to avoid copper deficiency (ATSDR 2004, WHO 1998 and 2002). Age-specific 'normative requirements' are given by WHO as 1.35mg/day for an adult male and 1.15mg/day for an adult female. Estimates of typical copper intakes (mainly through food, less by inhalation) for the EU population are in the range of 0.8–1.8mg/day. Typical copper intakes of men are higher than those of women while the intake among the general adult population is higher than that of the elderly. Intakes of both men and women are generally close to the WHO normative requirements but may be somewhat lower in specific locations where background levels of copper are unusually low (Sadhra et al 2007). The uptake of copper by the gastrointestinal tract is regulated homeostatically by specific mechanisms, which reduce absorption at higher exposure levels by enhancing faecal elimination. The oral absorption rate is usually in the range of 20–60%. *In vitro* studies with copper compounds (chloride or sulphate) as well as *in vivo* dermal application of copper salts or dermal exposure to metallic copper fumes

suggest that copper is poorly absorbed through the skin. After absorption, copper is transported by the blood (bound to ceruloplasmin and albumin) mainly to the liver and, to a lesser extent, to the kidney. The predominant elimination pathway is the bile. Small amounts are excreted via urine. Specific population groups with genetic defects or abnormalities in the metabolism of copper (eg individuals with Menkes disease or Wilson disease) may be sensitive to levels of copper exposure that are non-toxic to persons without these defects (ATSDR 2004, WHO 1998 and 2002)." (References cited SCOEL, 2014).

The DFG MAK Value Documentation on copper and its inorganic compounds noted:

"In an inhalation study carried out according to OECD Test Guideline 412 with Sprague Dawley rats exposed to Cu_2O in whole-animal chambers (see Section "Subacute, subchronic and chronic toxicity"), the copper concentrations in the lungs, broncho-alveolar lavage, liver and brain were investigated after exposure to 0, 0.17, 0.35, 0.7 or 1.7mg copper/m^3 for 4 weeks. In addition, the copper concentrations were determined after exposure for 1 to 3 weeks and after a 13-week recovery period in the controls and the high concentration group. In the lungs, the copper concentration was less than 2.50**µg/g** tissue (detection limit) in nearly all animals after exposure to 0.7mg copper/m^3. After exposure for 1 to 4 weeks to 1.7mg copper/m^3, the concentrations were 4.23 to 5.09 and 4.44 to 6.87µg/g lung tissue in the male and female animals, respectively. The highest concentrations were found after exposure for 1 to 2 weeks. In the BAL of rats exposed to 1.7mg copper/m^3, the highest concentrations were 400 and 458**ng/ml** after 1 week in male and female animals, respectively, the lowest were 204 and 243ng/ml after 3 weeks. After 0.7mg copper/m^3 and above, the concentrations in the BAL were below the detection limit of 100ng copper/ml after 4 weeks, while after exposure to 1.7mg copper/m^3 they were 232ng/ml in the male animals and 347ng/ml in the females.

"After a 13-week recovery period, the concentrations in the lungs and the BAL were below the respective detection limits. In the liver, after exposure for 1 to 4 weeks, slightly increased copper concentrations could be demonstrated only at 1.7mg copper/m^3. After 4 weeks these concentrations were 7.58µg/g in male rats and 7.64µg/g in female rats (controls 6.6 and 6.64 µg/g, respectively). The increase was no longer statistically significant 13 weeks after the end of exposure: 5.82µg/g (males) and 6.63µg/g (females) compared with values of 5.06 and 6.48µg/g in the controls. The highest values occurred after exposure for 1 week to 1.7mg copper/m^3, which shows that copper does not accumulate in the liver. In the brain, no increase in the copper concentration was found in any of the groups after exposure for 1 to 4 weeks (**ICA** 2010)." (References cited in DFG, 2015).

The SCOEL recommendation on copper and its inorganic compounds summarised some of the mechanistic data for copper toxicity:

"Nevertheless, besides its essential functions, copper ions may exert toxic properties on conditions of disturbed homeostasis due to overload or other than oral exposure routes such as inhalation. Thus, ionic copper binds with a high affinity to histidine or sulphur in cysteine and methionine. This can lead to inactivation of proteins and enzymes (Rae et al 1999). Reactive copper(II) can oxidise thiol groups located in the membranes to form disulphides, thereby

being able to disturb structural or functional properties of membranes (Kumar et al 1978). The copper(I) thus formed can be oxidised again to form copper(II) via endogenous oxygen or via hydrogen peroxide from the respiratory chain. In this redox cycle, reactive oxygen radicals can be produced through Fenton-like reactions (Goldstein and Czapski 1986). Therefore, it is assumed that reactive copper can lead to oxidative cell damage, such as lipid peroxidation, thiol oxidation, and DNA damage (Stark and Glass 1997, Li and Trush 1993).

"With respect to potential mechanisms involved in respiratory toxicity, Gu and Lin (2010) showed that copper (as $CuCl_2$) stimulated pulmonary sensory neurons via a direct activation of TRPA1 in pulmonary C-fibre sensory nerves in mice.

"Several studies support a high toxicity of copper oxide (CuO) nanoparticles in comparison to other metal oxide nanoparticles in pulmonary epithelial cells *in vitro* and also when compared to CuO microsize particles or water soluble copper salts (Karlsson et al 2008 and 2009, Fahmy and Cormier 2009, Lanone et al 2009, Ahamed et al 2010). Effects appear to involve sustained oxidative stress possibly due to redox cycling (Fahmy and Cormier 2009). One key mechanism may be the ability of CuO to damage the mitochondria (Karlsson et al 2009). Furthermore, **Hsp70**, p53 and DNA damage repair proteins Rad51 and MSH2 expression and/or protein levels were upregulated, demonstrating that CuO nanoparticles possess a genotoxic potential in A549 cells which may be mediated through oxidative stress (Ahamed et al 2010)." References cited SCOEL, 2014).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows copper exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

	COPPER, FUME, RESPIRABLE DUST		COPPER, DUSTS AND MISTS	
JURISDICTION OR ADVISORY BODY	**8-HOUR LIMIT VALUE**	**SHORT-TERM LIMIT VALUE**	**8-HOUR LIMIT VALUE**	**SHORT-TERM LIMIT VALUE**
	mg/m³	mg/m³	mg/m³	mg/m³
Australia	0.2		1	
Austria	0.1	0.4	1 5	
Belgium	0.2		1	
Canada – Ontario	0.2		1	
Canada – Québec	0.2		1	
Denmark	0.1	0.2	1	2
Finland	0.02[1,2]			
France	0.2		1	2
Germany – DFG	0.01 2	0.02[2,3]	0.01[2]	0.02[2,3]
Hungary	0.1	0.4	1	4
Ireland	0.2		1	
New Zealand	0.2		1	
People's Republic of China	0.2		1	
Poland	0.1	0.3	1	2
Romania		0.2[4]	0.5	1.5[4]
Singapore	0.2		1	
South Korea	0.1		1	2
Spain	0.2		1	
Sweden	0.2		1	
Switzerland			0.1[5]	0.2[5]
The Netherlands			0.1[5]	
USA – OSHA	0.1		1	
UK	0.2		1	2

TABLE 3:
Exposure standards for copper, fume, respirable dust and copper, dusts and mists from around the world

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on copper were SCOEL, Safe Work Australia, DFG and ACGIH®.

[1] Calculated as Cu.

[2] Respirable fraction.

[3] 15 minutes reference period.

[4] 15 minutes average value.

[5] Inhalable fraction/aerosol.

5.2 SCOEL

The Scientific Committee on Occupational Exposure Limits [SCOEL] assessment of copper and its inorganic compounds recommended an **OEL** of 0.01mg/m³ for the respirable fraction, based on all available evidence, and since the value was based on a NOAEC of 0.008mg/m³ in humans and the calculation of a human equivalent concentration (**HEC**) obtained from the 28-day inhalation study in rats, no further safety factors were included. SCOEL noted that the recommended OEL does not apply to copper nanoparticles due to their particularly high toxicity in pulmonary epithelial cells (SCOEL, 2014).

The rationale for their conclusions was:

> "The critical effect of inhalation exposure to copper is the local action on the respiratory tract, which includes an immunosuppression that is attributable to the disturbance of alveolar macrophage function."
>
> "The database includes studies conducted with a range of Cu compounds, including Cu_2O which is rapidly oxidised to CuO (ICA 2010). However, no sufficient data are available to recommend OELs for defined copper species and metallic copper, and therefore, this recommended OEL applies to copper and all its inorganic compounds. This approach is supported by the fact that poorly water soluble and water soluble copper compounds appear to be equally toxic in the few experimental inhalation studies available. It has to be noted that the OEL recommended for the respirable fraction does not apply to copper nanoparticles, which exert a particularly high toxicity in pulmonary epithelial cells (Karlsson et al 2008 and 2009, Fahmy and Cormier 2009, Lanone et al 2009, Ahamed et al 2010); however, no quantitative data suitable for risk assessment are available. Nevertheless, ultrafine copper particles may well have been present in the Gleason study, but the percentage of these small particles cannot be estimated.
>
> "With regard to a potential OEL for the inhalable fraction, a subacute inflammation in the nose was observed in one male rat at 0.17mg/m³ (ICA 2010). However, a final evaluation of this effect to derive a recommendation for an OEL for the inhalable fraction is not possible, since (1) only 5 animals were investigated per group, (2) an increase with time cannot be excluded because no animals were affected at interim section (3 weeks) up to 1.7mg/m³; (3) the study was conducted with the respirable fraction and one would expect a higher deposition in the nose with an inhalable fraction. Another approach consists in the consideration of the upper tolerable intake level for copper presented by the Scientific Committee on Food (**SCF**, today **EFSA**). SCF derived a tolerable upper intake of 5mg/day for adults. Daily intakes of copper from food in EU countries ranged from mean values of 1.1mg/day (the Netherlands) to 2.2mg/day (Germany) with the highest 97.5% upper confidence limit of 4.2mg/day (Austria) (SCF 2003, see Annex 1). Assuming an oral absorption rate of 30–40%, which is typical for diets in developed societies (SFC 2003), and an assumed 100 % absorption by inhalation, the daily difference of 0.8mg/day would correspond to an inhalable air concentration of copper of 0.03–0.04mg/m³ (5 days exposure/week with a breathing volume of 10m³/8-hour day). To avoid systemic toxicity, the inhalable exposure to copper should be below this value.
>
> "A NOAEC of 0.36mg/m³ has been estimated for acute sensory irritation in humans. It is not known, whether metal fume fever-like symptoms observed in employees exposed to copper dust at 0.12–0.36mg/m³ is primarily dependent on concentration or on total dose (concentration × time product). Given all the uncertainties, a scientifically based STEL cannot be recommended."

> "At the recommended OEL of 0.01mg/m³, no developmental effects are expected to occur. The lowest effect dose is that for postnatal developmental delay in the offspring of mice exposed to 1.3–1.6mg Cu/kg bw and day as copper sulphate (Kasama and Tanaka 1988, cited in WHO 1998). This dose corresponds to an air concentration of about 3–4mg Cu/m³ (assuming an oral absorption of 30–40% and 100 % absorption by inhalation, 70kg body weight and 10m³ breathing volume of the worker), showing that the difference is sufficiently large (300-fold) between the lowest NOAEL for developmental effects of 1.3mg/kg bw and the recommended OEL of 0.01mg/m³."
>
> "A clastogenic action of copper compounds cannot be excluded, but the data are inconsistent. The carcinogenic potential of copper cannot be evaluated on the basis of existing studies." (References cited in SCOEL, 2014).

The SCOEL assessment of copper and its inorganic compounds also noted that the extensive use of copper and its compounds and the small number of case reports, there is little concern about the sensitising properties of copper; that a "**skin**" notation was not recommended as the dermal uptake of copper compounds was considered to be low; and that Biological Limit Values could not be derived for several physiological reasons (SCOEL, 2014).

5.3 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] MAK Value Documentation on copper and its inorganic compounds recommended a MAK Value of 0.01mg/m³ for the respirable fraction, based on all available data (DFG, 2015).

The rationale for their conclusions was:

> "The local effects on the respiratory tract are the critical effects after inhalation exposure to copper."
>
> "In an earlier investigation in workers exposed to fine copper particles in concentrations of 0.12 to 0.36mg/m³, influenza-like symptoms were observed. The effects did not occur at copper concentrations of 0.008mg/m³ (Gleason 1968). After the exposure of mice to copper sulfate for 5 or 10 days and the simultaneous inhalation of streptococci, pulmonary defence mechanisms were reduced in a dose-dependent manner after copper concentrations of 0.12 and 0.13mg/m³ and above, respectively (Drummond et al. 1986). In a 4-week inhalation study (ICA 2010) carried out according to OECD Test Guideline 412 with whole-body exposure of Sprague Dawley rats to Cu2O, marked inflammatory reactions in the lungs occurred even at the lowest concentration tested of 0.2mg/m³ (0.17mg copper/m³).
>
> "The HEC (human equivalent concentration) calculated on the basis of this study assuming a **NAEC** (no adverse effect concentration) of 0.067mg Cu_2O/m³ (1/3 of the **LOAEC** (lowest observed adverse effect concentration)) for the rat, yielded a NAEC for humans of 0.012mg copper/m³ (see Appendix).
>
> "The studies with workers (Gleason 1968), the 28-day rat inhalation study (ICA 2010) and the 5 or 10-day inhalation study in mice of Drummond et al. (1986) are in agreement regarding the target organ (the lung, and in particular the alveolar macrophages), and produced marked effects in the same concentration range (0.12–0.36mg copper/m³). Even if no NOAEC is available from the animal studies, the study of Gleason (1968) in workers indicates that no effects are to be expected at copper concentrations of 0.008mg/m³."

> "Overall, on the basis of the presently available data, neither irritating effects in the nose nor systemic overloading nor adverse effects on the lungs can be excluded at a concentration in the air of 0.1mg/m³. As, for this reason and because of the described uncertainties, no value for the inhalable fraction can be derived, the previous MAK value of 0.1mg/m³ for the inhalable fraction has been withdrawn; nevertheless, in order to avoid copper overloading and potential systemic toxicity, exposure concentrations should be kept greatly below this value." (References cited in DFG, 2015).

The DFG MAK Value Documentation on copper and its inorganic compounds also noted that lack of data on dermal absorption precluded assigning an "**H**" designation; as there were no clinical observations in humans or findings from animal experiments from which skin or respiratory sensitisation from copper and its inorganic compounds might be derived, copper and its inorganic compounds were not designated with either "**Sh**" or "**Sa**"; and, as the 790-fold difference between the calculated NOAEC for developmental toxicity for rabbits and the MAK value of 0.01mg copper/m³ for the respirable fraction is sufficiently large, the classification of copper and its inorganic compounds in **Pregnancy Risk Group C** has been retained (DFG, 2015).

5.4 ACGIH®

The American Conference of Governmental Industrial Hygienists [ACGIH®] review of copper recommended a **TLV-TWA** of 0.2mg/m³, as Cu, for copper fume and a TLV-TWA of 1mg/m³, as Cu, for copper dusts and mists to minimise the potential for ocular, dermal, respiratory tract and mucous membrane irritation, and systemic effects that include gastrointestinal distress and conditions similar to metal fume fever (ACGIH®, 2001).

The rationale for their conclusions was:

> "Concentrations of copper fume from welding operations of 1-3mg/m³ of air for short periods resulted in altered taste response but no nausea; levels of from 0.02 to 0.4mg/m³ did not cause complaints (Whitman, 1957). Gleason (1968), however, found a condition similar to metal fume fever in workers exposed to metallic copper dust in concentrations of the order of 0.1mg/m³. Extensive industrial experience with copper-welding operations and copper-metal refining in Great Britain support the view that no ill effects result from exposure to fumes at concentrations up to 0.4mg of copper/m³ (Luxon, 1972).
>
> "Inhalation of dusts and mists of copper salts can result in irritation of nasal mucous membranes, sometimes of the pharynx, and on occasion, ulceration with perforation of the nasal septum. If copper salts reach the gastrointestinal tract in sufficient concentration, they act as irritants producing salivation, nausea, vomiting, gastric pain, hemorrhagic gastritis, and diarrhea." (References cited in ACGIH®, 2001).

5.5 Safe Work Australia

Safe Work Australia proposed a TWA of 0.01mg/m³ to protect for irritant and lung effects across various states in exposed workers (Safe Work Australia, 2019).

Their rationale was:

> "The critical effect associated with inhalation is local irritation of the respiratory tract. Concentrations of metal copper dust in the order of 0.1mg/m³ are reported to be associated with a condition similar to metal fume fever.

A study in workers reports a NOAEC of 0.008mg/m^3 for influenza-like symptoms (DFG, 2015). A four week inhalation study in rats identified a LOAEC of 0.17mg/m^3 reported for marked inflammatory reactions in the lungs (ACGIH, 2018; DFG, 2015; SCOEL, 2014). DFG (2015) and SCOEL (2014) derived a human equivalent NOAEC of 0.012mg/m^3 and 0.016mg/m^3, respectively.

Given the observed NOAEC in humans of 0.008mg/m^3 and supported by the derived human equivalent NOAECs from animal studies (SCOEL, 2014), a TWA of 0.01mg/m^3 is recommended to protect for irritant and lung effects across various states in exposed workers". (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne copper

A common method to determine the concentration of airborne copper is a modification of NIOSH Method 7303.

The filter is analysed by inductively-coupled plasma – atomic emission spectroscopy (**ICP-AES**). The limit of quantification of this modified method has been quoted as 1.5µg (or 0.0015mg) of copper per sample.

Collecting an air sample for 8 hours at a flow rate of 2.5**L/min** would allow a minimum concentration of less than 0.001mg of copper per cubic metre of air to be measured based on the quoted limit of quantitation.

Note: The reader's attention is drawn to section 1.6 of the 11th Edition of the special guide Workplace exposure standards and biological exposure indices, for advice in relation to recent research indicating that some sampling devices may result in oversampling when used at the historically recommended flow rates.

7.0
Discussion

WorkSafe's WES for copper has been unchanged since adoption in 1994.

The toxicological database reviewed above indicates copper fume, dusts and mists are locally and systemically toxic to humans, causing irritation of the mucous membranes and respiratory tract, immunosuppression, liver, kidney and cardiovascular toxicity; and is locally and systemically toxic to laboratory species causing similar effects.

Based on the aforementioned documentation, informed by the conclusions of the SCOEL, Safe Work Australia, DFG and ACGIH® reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 0.2mg/m³, for inhalable fraction of copper fume and a WES-TWA of 1mg/m³, for inhalable fraction of copper dusts and mists to be inadequate to manage health risks from possible workplace exposure:

- For workers exposed to fine copper particles in concentrations of 0.12 to 0.36mg/m³, influenza-like symptoms were observed, and the NOAEC of 0.008mg/m³ was reported (Gleason 1968 cited in SCOEL, 2014; DFG, 2015).
- Mice exposed to aerosols of copper sulphate at 0.12mg/m³ for 3 hours/day for 5 days or at 0.13mg/m³ for 3 hours/day for 10 days revealed a time-dependent immunosuppressive effect in the lungs (Drummond et al., 1986 cited in SCOEL, 2014; DFG, 2015).
- Rats exposed, whole-body, to aerosols of copper(I) oxide for 5 hours/day, 5 days/week for 4 weeks revealed inflammatory effects in the lungs with a LOAEC of 0.17mg/m³ (ICA, 2010 cited in SCOEL, 2014; DFG, 2015). DFG calculated a human equivalent concentration [HEC] for a human **$NOAEL_{HEC}$** of 0.012mg Cu/m³ (DFG, 2015).
- The SCOEL assessment of copper and its inorganic compounds recommended an OEL of 0.01mg/m³ for the respirable fraction, based on the NOAEC of 0.008mg/m³ reported in workers and the calculated NOAELHEC of 0.012mg Cu/m³ (SCOEL, 2014).
- The DFG MAK Value Documentation on copper and its inorganic compounds recommended a MAK Value of 0.01mg/m³ for the respirable fraction, based on the NOAEC of 0.008mg/m³ reported in workers and the calculated NOAELHEC of 0.012mg Cu/m³ (DFG, 2015).
- Safe Work Australia reports that concentrations of metal copper dust in the order of 0.1mg/m³ are reported to be associated with a condition similar to metal fume fever, and that a study in workers reports a NOAEC of 0.008mg/m³ for influenza-like symptoms (DFG, 2015).
- The SCOEL and DFG recommended OELs are for respirable fraction as the critical effect is local action on the respiratory tract including immunosuppression attributable to disturbance of alveolar macrophage function (SCOEL, 2014; DFG, 2015).

- SCOEL noted that the recommended OEL does not apply to copper nanoparticles due to their particularly high toxicity in pulmonary epithelial cells (SCOEL, 2014); and, DFG excluded nanoparticles from their evaluation (DFG, 2014).
- SCOEL and DFG noted that available data was inadequate to recommend an OEL/MAK Value for the inhalable fraction, but that to avoid copper overloading and systemic toxicity inhalable fraction concentrations should be kept respectively below 0.03–0.04mg/m^3 or 0.1mg/m^3 (SCOEL, 2014; DFG, 2015).
- SCOEL noted that available data was inadequate to recommend a STEL, due to uncertainties if peak concentration or total cumulative dose was responsible for acute sensory irritation in humans (SCOEL, 2014).
- The proposed WES-TWA for copper and its inorganic compounds of 0.01mg/m^3 [respirable fraction] is set to be protective against all non-carcinogenic endpoints, based on the NOAEC of 0.008mg/m^3 and calculated NOAELHEC of 0.012mg Cu/m^3 (SCOEL, 2014; DFG, 2015).
- A *skin notation* is not justified for copper, based on the expected limited absorption after dermal exposure (SCOEL, 2014; DFG, 2015).
- A ***sen*** *notation* is not warranted for copper, based on the lack of positive reports of human cases or from experimental animal studies (DFG, 2015).

8.0 Recommendations

WorkSafe considers its current WES-TWA of 0.2mg/m^3 for inhalable fraction of copper fume and a WES-TWA of 1mg/m^3 for inhalable fraction of copper dusts and mists to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. extend the WES to cover copper and its inorganic compounds
2. adopt a WES-TWA for copper and its inorganic compounds of 0.01mg/m^3, as Cu [respirable fraction].

Noting that the recommended WES-TWA of 0.01mg/m^3, as Cu [respirable fraction] may not eliminate all risk if the exposures contain copper nanoparticles.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
ADME	Absorption, Distribution, Metabolism and Excretion.
ADP	Adenosine diphosphate.
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
CD4+	T helper cells [T_h cells].
CHO	Chinese hamster ovary.
Cu	Copper.
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DMSO	Dimethyl sulphoxide.
DNA	Deoxyribonucleic acid.
EC_{50}	Effective Concentration 50%: Concentration resulting in 50% response.
EFSA	European Food Safety Authority.
EPA	The New Zealand Environmental Protection Authority.
EU vRAR	European Union voluntary Risk Assessment Report – EC documentation.
FEV1	Forced expiratory volume in 1 second.
Fume	Fumes are very small airborne solid particulates with diameters generally less than 1µm. They may be formed by both thermal mechanisms (eg condensation of volatilised solids, or incomplete combustion) and chemical processes (eg vapour phase reactions). Agglomeration of fume particles may occur, resulting in the formation of much larger particles.
"H"	DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the 'skin' notation in the WorkSafe WES Special Guide.
HEC	Human equivalent concentration.
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.
Hsp70	70 kilodalton heat shock proteins (Hsp70s or DnaK) are a family of conserved ubiquitously expressed heat shock proteins.
IARC	The International Agency for Research on Cancer – an agency of the World Health Organisation.
ICA	International Copper Association.
ICP-AES	Inductively-coupled plasma atomic emission spectroscopy – a method used in analytical chemistry to detect metals and some non-metal species.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly <100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009). (*cf*. Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter).

TERM	MEANING
LC50	Lethal Concentration for 50% of the test population.
LD50	Lethal Dose for 50% of the test population.
LLNA	Local lymph node assay.
LOAEC	Lowest Observed Adverse Effect Concentration.
LOAEL	Lowest Observed Adverse Effect Level.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (eg by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
µm	Micrometre or one millionth of a metre.
µM	Micromolar of a substance that is equal to µmol/L.
µmol/l	Micromole of substance per litre of the matrix.
µg/g	Microgram or one millionth of a gram per gram of the matrix.
mg	Milligram or one thousandth of a gram.
mg/kg	Milligrams per kilogram.
mg/kg bw	Milligram of substance per kilogram body weight.
mg Cu/kg bw	Milligram of copper per kilogram body weight.
mg Cu/ kgBW/day	Milligram of copper per kilogram body weight per day (exposure rate).
mg/m^3	Milligrams of substance per cubic metre of air.
mM	Millimolar of a substance that is equal to mmol/L.
mmol/l	Millimole of substance per litre of the matrix.
MR	Mean reaction score.
MSH2	DNA mismatch repair protein Msh2 also known as MutS protein homolog 2 or MSH2.
NAEC	No adverse effect concentration.
ng/mL	Nanogram of a substance per millilitre.
NLM	National Library of Medicine, administered by the US National Institutes of Health.
NOAEC	No Observed Adverse Effect Concentration.
NOAEL	No Observed Adverse Effect Level.
$NOAEL_{HEC}$	No Observed Adverse Effect Level, human equivalent concentration.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
OEL	Occupational Exposure Limit (equivalent to a WES).
p53	Also known as TP53 or tumour protein (EC :2.7.1.37) is a gene that codes for a protein that regulates the cell cycle and hence functions as a tumour suppression. It is very important for cells in multicellular organisms to suppress cancer.
ppm	Parts of vapour or gas per million parts of air.

TERM	MEANING
Pregnancy Risk Group C	Damage to the embryo or foetus is unlikely when the MAK value or the BAT value is observed. A DFG term.
Rad51	In humans, RAD51 is a 339-amino acid protein that plays a major role in homologous recombination of DNA during double-strand break repair.
RoC	Report on carcinogens.
"Sa"	Sensitising to airways. A DFG MAK notation.
SCF	Scientific Committee on Food, now European Food Safety Authority [EFSA].
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
sen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
"Sh"	DFG MAK designation: *danger of sensitisation of the skin*.
SI	Stimulation Index.
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term.
SOS	SOS response is a global response to DNA damage in which the cell cycle is arrested and DNA repair and mutagenesis are induced.
STEL (WES-STEL)	The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-TWA	TLV® – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-STEL	The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.
WHO	World Health Organisation, Geneva.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

Appendix 3: References

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Notes

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