

Copper

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Copper

- ▶ Cu is both a toxic and **essential element** for living systems.
- ▶ Cu occurs as part of the prosthetic group of proteins.
- ▶ It is an essential trace element, being the **third most abundant trace element** in the body, and is an important **catalyst** for haeme synthesis and iron absorption.
- ▶ As a cofactor for the enzyme Cu/Zn superoxide dismutase, Cu **protects against free radical damage** that may affect proteins, membrane lipids, and nucleic acids.

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- ▶ It is necessary for enzymes involved in **aerobic metabolism**, such as cytochrome c oxidase in mitochondria
 - ▶ Cu deficiencies have been linked to **mental retardation**, **anemia**, **hypothermia**, **bone fragility**, and impaired cardiac, neuronal, and **immune functions**

Physical Appearance

- ▶ Copper is a lustrous, ductile, malleable, odourless solid with a distinct **golden-red or reddish-brown colour**.

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- ▶ **Copper salts produce toxicity**
 - ▶ **Metallic copper itself probably has little or no toxicity**

Uses

Elemental Copper:

- ▶ Copper has excellent electrical conductivity, corrosion resistance, malleability and ductility, which make it very useful as an **industrial metal**.
- ▶ Copper whiskers are used in **thermal and electrical composites**
- ▶ Used in important **alloys such as bronze & brass**
- ▶ Another copper alloy (money metal), is copper **alloyed with nickel**
- ▶ useful in **electroplated coatings and undercoatings** for products made from nickel, chromium, and zinc, and in **cooking utensils**.
- ▶ Made into **corrosion-resistant plumbing pipes**, used in heating and roofing materials for building construction.
- ▶ As **intrauterine contraceptive devices**

Uses

Copper Compounds:

- ▶ **Copper oxide**: (Cupric & Cuprous oxide) as catalyst and a pigment for **ceramic, glass, enamel, and porcelain**. Used in copper metallurgy, pyrotechnics and welding and in the manufacture of rayon. found in batteries, electrodes, desulfurising oils, paints fungicides and insecticides.
- ▶ **Copper acetate**: paint pigment, insecticide, and fungicide
- ▶ **Copper carbonate**: used in pigments, pyrotechnics, insecticides, fungicides and brass colouring
- ▶ **Copper chloride**: used as a disinfectant, in metallurgy, for the preservation of wood pulp, in photography, in water purification, and as a feed additive.
- ▶ **Copper nitrate**: Used in pharmaceutical preparations and in paints, varnishes and enamels
- ▶ **Copper cyanide**: Used in the electroplating of copper on iron.

Uses

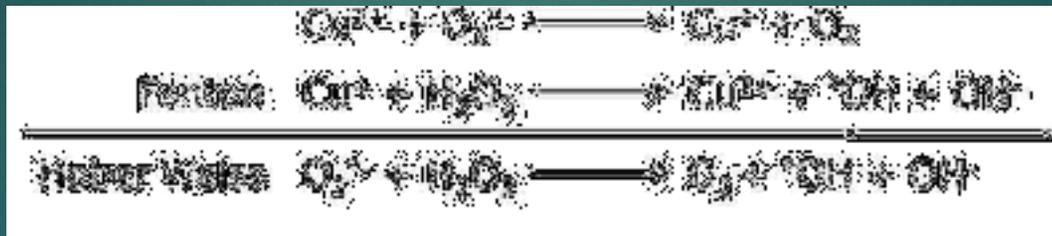
- ▶ **Copper sulfate/sulfide**: used as a fungicide, molluscicide and wood preservative, for water treatment as a bactericide and algaecide, as a mordant, in leather tanning and hide preservation, and in some fertilisers.
- ▶ Used medicinally as an **emetic**, and in several intrauterine contraceptive devices.

Usual Fatal Dose

- ▶ About **10 to 20 grams** of copper sulfate
- ▶ The daily adult requirement of **2mg** is supplied in a normal diet.
- ▶ Ingestion of more than **250 mg of copper sulfate can produce vomiting**, and larger ingestions can potentially cause hepatic and renal injury
- ▶ **Water**; The US Environmental Protection Agency (EPA) has established a safe limit of **1.3 mg/L in drinking water**.
- ▶ Inhalation-The recommended workplace limit for copper fumes is **0.2 mg/m³ for dusts and mists**, it is **1 mg/m³**
- ▶ The air level considered immediately dangerous to life or health for dusts or fumes is **100 mg Cu/m³**

Mechanism of toxicity

- Copper toxicity is a consequence of the generation of **reactive oxygen species (ROS)** and lysosomal lipid peroxidation leading to cell death by copper ions via Fenton or Haber-Weiss reactions



- Copper ions display high affinity for **thiol and amino groups** occurring in proteins.
- Thus, specialized proteins containing clusters of these groups transport and store copper ions, hampering their potential toxicity.

Mechanism of toxicity

This mechanism, however, may be overwhelmed under copper overloading conditions, in which copper ions may bind **to thiol groups occurring in proteins non-related to copper metabolism.**

Indiscriminate copper binding may lead to **damaging consequences to protein structure, modifying their biological functions**

Toxicokinetics

▶ Prepare Toxicokinetics



Clinical presentation

▶ Acute Poisoning:

Ingestion

- ▶ Myalgia, abdominal pain, vomiting (bluish or greenish),* diarrhoea, acidosis, pancreatitis, methaemoglobinaemia, haemolysis, jaundice, oliguria, renal failure, seizures, delirium and coma
- ▶ Hepatomegaly, liver tenderness, increased levels of transaminase and jaundice may occur on the second or third day
- ▶ Acute copper sulfate or copper salts intoxication can lead to Intravascular haemolysis which can further lead to Acute renal failure (develops in 20 to 40 percent)

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- ▶ **Anuria or oliguria may develop 24 to 48 hours after ingestion with increased BUN**

Inhalation

- ▶ **Inhalation of copper dust or fumes can cause cough, sore throat, and conjunctivitis, while copper oxide can lead to metal fume fever syndrome.**

Eye exposure

- ▶ **Conjunctivitis**
- ▶ **corneal ulceration**
- ▶ **Turbidity as well as palpebral oedema**
- ▶ **Chalcosis lentis –can lead to uveitis, abscess, serious injury or loss of the eye & sometimes may dissolve and disseminate to the lens, cornea and iris, where it may produce a greenish brown discolouration of the anterior capsule visible by slit-lamp microscope.**

Clinical presentation

Chronic Poisoning

- ▶ **Insecticide in vineyards-Vineyard sprayer's lung disease (histiocytic granulomatous lung)**
- ▶ **Swimming pool water containing algicidal copper-green hair discolouration**
- ▶ **“spiritual green water” to devotees (Church) which contains copper sulfate. When this is ingested, serious toxicity and even death can result.**
- ▶ **Cooking in copper or brass vessels can cause copper poisoning**

- ▶ **Chronic copper toxicity is the hallmark of Wilson's disease an autosomal recessive genetic disorder in which there is deficiency of caeruloplasmin**

Wilson's disease

- ▶ **Kayser-Fleischer ring-deposition of copper in parenchymal tissue. A 'sunflower-like' discoloration of the most anterior layers of the lens**

Inhalation

- ▶ **Metal fume fever, wheezing and rales with fine copper dust.**
- ▶ **Dyspnoea has developed after oral copper exposure**

Skin exposure can produce severe irritation, itching, erythema, dermatitis and eczema

Kayser-Fleischer ring



Diagnosis

- ▶ **Serum caeruloplasmin level:** A value of 35 mg% or less at 24 hours is associated with serious toxicity.
- ▶ **Blood copper level:** If this is elevated beyond 1.5 mg/100 ml, there is likelihood of serious toxicity. Average normal levels are 1.09 mg/L for men, 1.20 mg/L for non-pregnant women and 2.39 mg/L for pregnant women.
- ▶ **Urine level:** Normal daily excretion of copper in the urine is less than 0.6 micromole/day.
- ▶ **Radiography:** Metallic copper is radiopaque. X-rays may be useful

Treatment

- ▶ Haemodialysis is said to be useful in the early stages of poisoning when the metal is still circulating in the bloodstream as free copper.
- ▶ Administration of egg white or milk orally may help in detoxifying copper resulting in the formation of an albuminate.
- ▶ Stomach wash can be done with a solution of **potassium ferrocyanide**. It converts the copper salt (especially copper sulfate) into insoluble cupric ferrocyanide.
- ▶ Induction of emesis is contraindicated.

Treatment

- ▶ There is little clinical experience in the use of chelators in the setting of acute copper intoxication. Data on efficacy is derived from patients with chronic copper intoxication and animal studies
- ▶ Chelation therapy is generally recommended in symptomatic patients.
- ▶ If asymptomatic, confirm with laboratory before giving chelation
- ▶ D-penicillamine is considered the drug of choice for Wilson's disease

Treatment

- ▶ **Adult Dose:** 1000 to 1500 mg/day divided every 6 to 12 hours, before meals.
- ▶ **Paediatric Dose:** Initially 10 mg/kg/day, gradually increase to 30 mg/kg/day divided in two or three doses as tolerated. Doses up to 100 mg/kg/day in four divided doses may be used depending on the severity of poisoning and adverse effects. Give before meals; maximum 1 gm/day.
- ▶ **Pregnancy:** Use of penicillamine in pregnancy has been associated with connective tissue abnormalities, hydrocephalus, cerebral palsy, cardiac and great vessel anomalies
- ▶ **Teratogenic effect** when used in low doses or for short periods of time, as in metal chelation, has yet to be determined

Treatment

- ▶ **Dimercaprol-Acute copper sulfate intoxication but data regarding efficacy are lacking.**
- ▶ **The usual dose is 3 to 5 mg/kg/dose deep IM every 4 hours for 2 days, every 4 to 6 hours for an additional 2 days, then every 4 to 12 hours for up to 7 additional days**
- ▶ **Unithiol is not FDA-approved in USA, but it has been used with beneficial effects by some investigators.**
- ▶ **The usual dose is 5% solution IM or SC 5 mg/kg three or four times during the first 24 hours, 2 to 3 times on day two, and 1 to 2 times daily thereafter**

Treatment

- ▶ **Calcium disodium edetate-acute copper sulfate intoxication but data regarding efficacy are lacking.**
- ▶ **The usual dose is 75 mg/ kg/24 hours deep IM, or slow IV infusion given in 3 to 6 divided doses up to 5 days; may be repeated for a second course after a minimum of 2 days; each course should not exceed a total of 500 mg/kg body weight**

Treatment

- ▶ **Symptomatic measures-antacids and ranitidine for prevention of gastric erosions, dopamine for shock**
- ▶ **Eye exposure-irrigate exposed eyes with copious amounts of room temperature 0.9% saline or water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist after 15 minutes of irrigation, an ophthalmologic examination should be performed**
- ▶ **Dermal exposure-Remove contaminated clothing and wash exposed area extremely thoroughly with soap and water**

Treatment

- ▶ **Monitor serum and urine copper concentrations in patients with significant dermal exposure.**
- ▶ **Chelation therapy should be considered if copper concentrations are excessive**
- ▶ **Disorder of hair colour-Use of shampoos containing penicillamine (250 mg in 5 ml of water and 5 ml of shampoo) or EDTA have been effective in removing green colour from hair due to copper exposure**