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Copper Toxicity And Its Medicolegal Aspects: A Review

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ABSTRACT: -

Copper may not be self-injected for sucidial or self harm because of the colour and taste. In most of cases accidental poisoning occurs. Accidental poisoning results from eating food contaminated with Verdigris which is formed from the action of vegetable acids on copper cooking vessels which are not properly tinned on the inside. A number of adverse health effects can result from excessive copper levels including damage to kidneys and liver, anemia, immuno-toxicity and developmental toxicity. Copper affects virtually everybody system directly or indirectly. Copper-mediated deficiency, or deficiency of vitamin C, folic acid, or other nutrients induced by copper toxicity, is responsible for many symptoms associated with copper toxicity. The aim of this review is to focus on the diagnostic difficulties facing coroners and forensic pathologists when the court reguire confirmation. Forensic examination performed on the corpses of victims who died in or out of hospital or on surviving injured or intoxicated victims showing signs of metal poisoning, demands the careful evaluation of the death scene, all related circumstances and of clinical and autopsy data. Close interaction between forensic pathologist and toxicologist is also needed to identify and quantify copper levels in blood, urine and tissues.

Keywords: Lethal intoxication, Heavy metal toxicity, Chronic poisoning, Copper sulphate

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INTRODUCTION:

Pure metallic copper is not poisonous, but copper salts are definitely poisonous, especially blue vitriol, also known as *nila thotha* and the verdigris. Copper is one among the well-known inhibitor of enzymes.[1] Copper is believed to have originated from Cyprus, where romans used to extract it from their rich copper mines. Its name copper originated from Latin word Cuprum (CU). It is a metallic element whose symbol is CU. Its atomic no. is 29 and its atomic weight is 63.546.[2] The accidental consumption or installation of contaminated water sources, copper salt-containing topical creams for burn treatments and acidic foods cooked in uncoated copper cookware are often the result of many instances of copper toxicity. Copper sulphate is an easily accessible chemical and is even sold over the counter. It is widely used in the leather industry, as a pesticide and in making home-made glue. Burning of copper sulphate in houses and shops is commonly practiced among Buddhists and Hindus.[3] Except widespread uses, copper is also an essential trace element and has a vital impact on the health of all living things (humans, animals, plants and microorganisms). Copper is an important trace element for the proper function of organs a metabolic process also required for proper enzymatic functions.[4]

It is rarely used for homicide because of the colour and taste. However, cases of using copper sulphate mixed with powdered glass, sweetmeat or some other food is known in India. In most of cases accidental poisoning occurs. Accidental poisoning results from eating food contaminated with Verdigris which is formed from the action of vegetable acids on copper cooking vessels which are not properly tinned on the inside. A number of adverse health effects can result from excessive copper levels including damage to kidneys and liver, anemia, immuno-toxicity and developmental toxicity.

Poisonous Compounds of Copper: [5,6]

The compounds of copper are copper sulphate (blue vitriol), copper subacetate (verdigris or zangal), copper arsenite and copper aceto arsenite (Scheele's green or Paris green). Of these, copper sulphate is the most common source of poisoning and in the line next comes copper sub-acetate. Copper sulphate is available as light blue crystal which when heated to 220·C-240·C becomes anhydrous and becomes white which is highly hygroscopic, draws water from atmosphere and again becomes blue. Copper subacetate is available as minute blue crystals and occurs when organic acid is treated with metallic copper. Most of common salts, including $CuSO_4$, has got a bitter, metallic, styptic taste. Copper sulphate is freely soluble in water and will impart the coloration whereas, copper subacetate is mostly soluble in fatty media.

S. N.	Poisonous Compounds	Common Name	Features
01	Copper sulphate	Blue vitriol, *Nilathotha* (Hindi)	Blue crystalline powder
02	Copper subacetate	Verdigris, Zangal	Green crystalline Powder
03	Copper aceto arsenite	Paris Green	Emerald green powder
04	Copper arsenite	Scheele's Green	Greenish powder
05	Copper corbonate	Mountain Green	Green crystalline powder

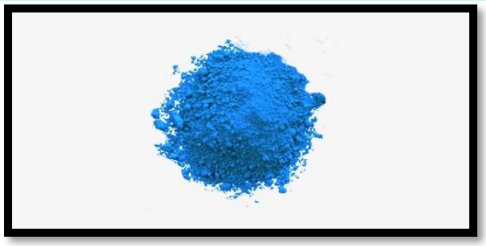

Figure-1 Copper sulphate

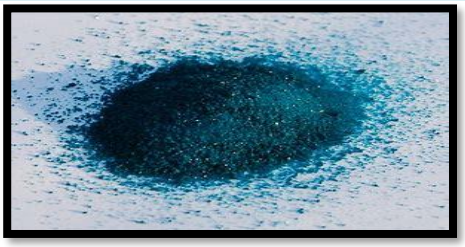

Figure-2 Copper subacetate

Widespread Uses [7]

- **Electrical Products-** such as electrical wirings, engine copper windings etc.
- **Alloys-**Copper is used in many brass and bronze alloys.
- **Used for Bullets-** Used as a jacket for nickel bullets.
- **Pesticides-** Many pesticides are produced with small quantities of copper or copper containing molecules.
- **Insecticides-** Molecules of copper used in insecticides.
- **Insect Repellents-** Used to repel insects.
- **Art Industries-** Used for many artistic designs to be prepared.
- **Cattle Poison-** CuSO4 has also been Used to kill the cattle's and for inducing abortion.
- **To Impart Rich Green Color-** In preserved and tinned peas and for other green vegetables.

Figure-3 Copper wires

Figure-4 Copper bullets

Figure-5 Copper tubes

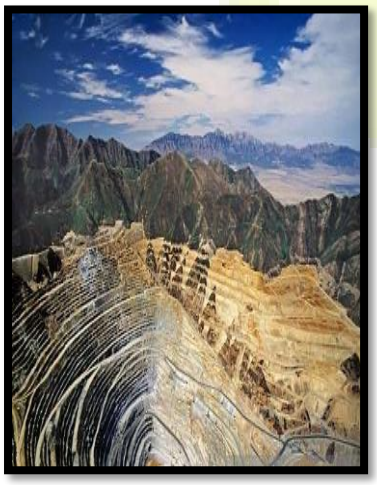

Figure-6 Copper mines

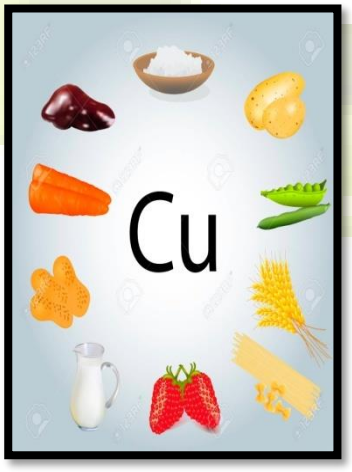

Figure-7 Copper rich foods

Figure-8 Copper coins

Medical Uses [8]

Of the several copper salts, copper sulphate ($cuso_4$) is primarily used for medical purposes.

- Copper sulphate solution is used to remove granulation tissue.
- In case of acute phosphorus poisoning 1% copper sulphate solution is used as an chemical antidote.
- It is used to prepare Fehling-solution for the detection of free sugar in urine.

Environmental Copper Exposure [9]

In the atmosphere, copper pollution comes from human activities and from natural sources. Excavation of copper mines produces dust rich in metal, and wind will scatter it around the mine site. Companies dealing with copper in the production of metals, electrical equipment, pesticides, fungicides and other copper containing goods often release polluted water in the drainage system that leads to streams and other water bodies. The use of pesticides also introduces more copper compounds into the atmosphere and may affect humans consuming unwashed fruits and vegetables sprayed with such pesticides. In buildings, copper used in plumbing dissolves gradually and aids the metal into the water supply. Other sources of water contamination include burning of fossil fuel, used motor oil, paint, wearing out of brake pads as well as certain birth control methods.

Occupational Copper Exposure [10]

Moderate exposure to copper takes place on a long-term basis in the case of workers working on a long-term exposure in many copper-handling industries. Evidence is accumulating about multiple health effects that arise after a long period of such exposures. Although copper is essential for good health, exposure to large doses of copper causes harm to human health. Long-term copper dust exposure can cause irritation of the nose, mouth and eyes and may also result in headache, dizziness, nausea and diarrhoea. Metal fume fever has been observed due to exposure of copper fumes. Other reported effects are hepatomegaly, digestive disorders and a range of respiratory signs and symptoms. The severity of effects of copper exposure are likely to increase with both level and length of exposure.

Other Sources of Copper Exposure [11]

1. **Copper Cookware:** If used frequently for period of time, copper tea kettles and other Copper cookware may be a source of copper toxicity.
2. **Birth Control Pills:** One of the side effects of the pill is that it tends to raise copper levels in the body. This is because of strong relation between the levels of hormone oestrogen and copper.
3. **Copper Intrauterine Devices:** Several hundred milligrams of copper a year can easily be absorbed from a copper IUD. Many women still use the Copper-T intrauterine birth control device, although it has been taken off the market. The only intrauterine birth control device sold today, however, is a copper-T. For women susceptible to high levels of copper, these devices can be very harmful.
4. **Vitamin and Mineral Supplements:** Copper is often added to vitamin supplements, especially prenatal vitamins. Although this is beneficial for certain people, it can be harmful for many other women.
5. **Fungicides for Swimming Pools and Foods:** Copper sulphate is added to swimming pools and may be sprayed on fruits and vegetables to inhibit growth of algae and fungus.
6. **Vegetarianism and Other High Copper Diets:** Many foods contain high levels of copper. In particular, vegetarian proteins such as soybeans, nuts, seeds, tofu, avocados and grains are especially high in copper content. Fast food burgers and other common foods are soy-based. Soybean protein is commonly used, due to its low cholesterol level and lower cost. Organ meats, shellfish, wheat germ and bran, yeast,

corn oil, margarine and mushrooms are other high grade copper foods.

7. **Dental Appliances:** Copper is used in dental alloys in fillings, crowns and other appliances.

Health and Copper Benefits [12]

Copper is a trace element, which is essential for our body. It is located in tissues of the body and plays a significant role in the production and maintenance of red blood cells, nerve cells and the immune system.

1. For body nutrition copper is an essential part.
2. It helps to build blood cells together with iron.
3. It maintains healthy blood vessels and bones.
4. Enough copper diet helps to prevent the incidence of cardiovascular diseases and osteoporosis.
5. An imbalance of copper can lead to Alzheimer's disease.
6. Hypertension and high cholesterol can result from low copper levels in the body.
7. Copper plays an important role to maintain collagen and elastin.
8. It helps to slow aging because of its antioxidant properties.

Absorption and Excretion [13, 14, 15]

Copper is normal constituent of body and normal copper content of the body is 150 mg. Safe daily intake of dietary copper is between 2 to 3 mg. Maximum absorption of copper occurs in the stomach and jejunum after ingestion. It is present in two forms – bound with albumin and other form bound with copper enzyme ceruloplasmin.

- Copper is absorbed through skin, GIT, lungs and mucous membrane and raw surfaces.
- It is excreted mostly by bowels than by the kidneys, through bile and traces are found in saliva and milk. The excretion of copper through urine is low in humans. Adults have urinary excretion of 25 g/24 h.µ.

Metabolic Effects of Copper [16]

Copper affects virtually every body system directly or indirectly. Copper also interferes with the function of adrenal and thyroid glands, producing other symptoms relating to hypothyroidism and adrenal insufficiency. Basic functions which are copper dependent include:

1. Formation of melanin and keratin.
2. Synthesis of connective tissue and myoglobin.
3. Synthesis of haemoglobin (incorporation of iron into haemoglobin).
4. Energy production (the electron transport system).
5. Synthesis of neurotransmitters (the catecholamines).
6. Free radical scavenging (superoxide dismutase).
7. Calcium storage in the bone matrix.
8. Immune system (reticuloendothelial cell formation and control of anaerobic organisms)
9. Formation of myelin nerve sheath.
10. Fertility and maintenance of pregnancy.

Metabolic Dysfunctions Associated with Copper Toxicity [17]

1. **Adrenal hypertrophy:** The adrenal glands dramatically increase in weight when the tissue levels of copper are high- which suggests excessive stress.
2. **Androgens:** A low level of copper in the body, particularly an elevated zinc and copper ratio, suggests increased secretion of androgen.
3. **Anaemia:** A high ratio of copper/molybdenum can lead to iron deficiency anaemias and may cause iron-storage disease.
4. **Calcium Level, Elevated:** A high calcium level above 120.00 mg% indicates a calcium bio unavailability. High levels of calcium are usually associated with elevated copper levels. An elevated calcium level is frequently the result of a manganese deficiency caused by elevated levels of copper.
5. **Cancer and High Tissue Copper:** Chronic tissue zinc and vitamin B6 deficiencies in adult life due to copper toxicity may predispose cells to cancerous modification. During active phases of the malignancies, the copper level increases

and fall down to normal limits during remissions.

6. **Cholesterol, Elevated:** When copper levels are relatively high in blood, fat levels decrease. Elevated lipid levels can be caused by any contaminant that depresses copper and zinc, such as cadmium in case of zinc.
7. **Depression, Mental:** Elevated tissue copper levels are often associated with mental depression an elevated level of copper decreases the levels of tissue manganese that can contribute to depression.
8. **Diabetes:** Diabetes is frequently associated with high tissue copper levels. Excess of copper frequently reduces zinc and manganese levels, thus interfering with glucose metabolism.
9. **Fears:** A wide range of fears are generally associated with elevated tissue copper levels.
10. **Headaches, Migraine:** Elevated copper levels are also associated with migraine headaches
11. **Heart Attacks:** A high level of tissue copper level predisposes one to hypertension, heart attacks and strokes by inducing a deficiency of zinc.
12. **Hodgkin's Disease:** Copper scores in Hodgkin's disease have proven to be a highly sensitive index.
13. **Hyperactivity, Childhood:** Both copper and iron are brain stimulants. Therefore each of these elements might play a role in the causation of hyperactivity and autism.
14. **Hypertension:** Excessive aldosterone hormone, produced by the adrenal cortex, is responsible for elevated blood pressure, by raising sodium levels.
15. **Kidney Disorders:** The complications of kidney are primarily due to displacement of zinc by copper.
16. **Libido (Decreased):** A high amount of tissue copper or a low zinc and copper ratio is also associated with a decreased libido.
17. **Myocardial Infarction:** In those who die from heart attacks, the copper level of the heart is higher than average. There is increased chance of heart attack among users of the birth control pill.
18. **Nervousness:** Elevated tissue copper levels are often associated with excessive biogenic amine levels and excess is frequently responsible for nervousness, hypertension, etc.
19. **Panic Attacks:** Copper toxicity is strongly associated with Panic attacks. Zinc deficiency may contribute to this problem due to copper excess.
20. **Sexual Inadequacy:** Sexual dysfunction is frequently the result of excess copper in the tissues.
21. **Tooth Decay:** High levels of lead, copper, zinc and chromium in the tissues of the body may increase the susceptibility of tooth decay.
22. **Urinary Tract Infection:** Elevated levels of copper are often related to urinary tract infections.

Mode of Action [18, 19]

Copper toxicity is exerted on enzymes whose activities depend on the groups of sulfhydryl and amino because it has high affinity for nitrogen and sulphur donor ligands.

It also inhibits the G-6-PD including glutathione reductase, reducing their free radical scavenging activities.

Copper increases the permeability of cell membranes by inhibiting the NA+ /K+ ATPase pump.

Signs and Symptoms [20]

1. Acute Poisoning

By Ingestion:

Symptoms appear in 15 to 30 minutes. Metallic taste, increased salivation, burning stomach pain with colicky abdominal pain, thirst, nausea, eructation’s and frequent vomiting are present. The vomited matter is blue or green. Motions are brown and liquid but not bloody, there is diarrhoea with much straining. Oliguria, uraemia, haematuria, albuminuria and acidosis may occur. Haemolysis,

haemoglobinuria, methemoglobinemia, jaundice, pancreatitis and cramps of legs or spasms and convulsions occur in serious cases. There is difficult breathing, cold perspiration and severe headache. In some cases, paralysis of limbs, insensibility, coma and death due to shock may occurs. Death occurs due to hepatic or renal failure.

By Acute Inhalation:

Acute inhalation of a large dose of copper dusts or fumes can lead to sore throat and cough caused by upper respiratory irritation. Conjunctivitis, palpebral oedema and sinus irritation may also occur. There may be nasal mucous membrane atrophy with perforation.

By Skin Exposure:

Skin exposure to copper compounds can lead to irritant contact dermatitis, and severe exposure of copper compounds can lead to greenish-blue discolouration of the skin.

2. Chronic Poisoning

It may occur in metal workers due to dust inhalation or food contaminated with verdigris. Chronic copper sulphate spray inhalation can cause vineyard sprayer's lung disease characterised by a histiocytic granulomatous lung. Wilson's disease is caused by chronic copper poisoning. Symptoms include gradual anaemia, green line on gums, nausea, vomiting, colic, diarrhoea, malaise, peripheral neuritis, muscle degeneration and atrophy. The presence of copper deposits in the tissues of the body is called CHALCOSIS. Copper may be deposited in the cornea causing a pigmented ring in the deeper layers. Chronic contact with water in the swimming pool containing algicidal copper chemicals can lead to green discolouration of the hairs.

Laboratory Investigations [21,22]

- **Ammonium hydroxide:** Produces a greenish-blue precipitate, that is excessively soluble and forms a blue solution.
- **Serum caeruloplasmin level:** Severe toxicity is associated with a value of 35 mg % or less over 24 hours.
- **Rubeanic acid evaluation:** ammonia is subjected to a drop of the neutral test solution on the filter paper. Add a drop of 1% rubeanic acid solution. Owing to presence of copper spot becomes olive green.
- **Blood copper level:** There is risk of severe toxicity if copper level elevated beyond 1.5 mcg/100 ml.
- **Neutron activation analysis:** Copper can be detected by neutron activation analysis and atomic absorption spectroscopy.
- **Hair analysis:** Hair analysis is a simple and easy screening test which can detect copper imbalance both direct and the hidden. A copper level more than 2.50 mg% is considered elevated.

With the advent of modern laboratory techniques, concentrations of trace elements can now be calculated with great accuracy and precision from the smallest of samples. In particular, since the invention of the multi-detection-capable inductively coupled plasma mass spectrometry (ICP-MS) method, hair tissue mineral analysis has become the diagnostic tool of choice because it can accurately and non-invasively excess the existence of nutritional and toxic elements.

Fatal Dose:[23]

- Copper sulphate: 20 g (0.15-0.3 g/kg).
- Copper subacetate, 15g.

Fatal Period:[24]

- 18-24 hrs, but it may extend to 1-3 days.

Treatment of Acute Copper Poisoning: [25, 26, 27]

1. **Stomach wash** with one percent potassium ferrocyanide solution, which forms an insoluble cupric ferrocyanide, acts as an antidote.
2. **Emetics** are contraindicated.
3. **Demulcent** drinks form insoluble albuminate of copper.

4. **Haemodialysis** is useful in the early stage of poisoning.
5. **Castor oil** is given to remove poison from intestines.
6. **Chelation** with penicillamine or EDTA or BAL.
7. **Maintain electrolyte** and fluid balance.
8. **Allay pain** by injecting morphine and use diuretics, if urine is suppressed.
9. **For severe cases** associated with anorexia and haematuria, cortisone 50-100 mg IM thrice daily is recommended.

Treatment of Chronic Copper Poisoning [28]

- First to remove the cause of poisoning and avoid further exposure.
- Provide fresh air.
- Give massage and warm bath.
- Provide proper diet.
- Copper vessels should be tinned and constantly kept scrupulously clean.

Post-mortem Appearances [29, 30,31]

1. The skin may be yellow.
2. There may be presence of Greenish-blue froth at mouth and nostrils.
3. The stomach contents and gastric mucosa are greenish or bluish in colour.
4. There may be congested, swollen, inflamed gastric mucosa, and occasionally eroded.
5. The liver may be soft and fatty.
6. There may also be mild to moderate irritation in upper part of small intestine.
7. Spontaneous haemolysis of blood and degenerative changes in proximal tubules of kidney may occur.
8. Ulceration or perforations can be seen in the colon and rectum.
9. In case of chronic poisoning, gums appear with bluish lining. There is mucosal atrophy. The liver and kidneys have various degree of degeneration.

Medicolegal Aspects [32, 33, 34,35]

1. It is rarely used for homicide because of the colour and taste. However, cases of using copper sulphate mixed with powdered glass, sweetmeat or some other food is known in India.
2. Copper coins when swallowed may remain in the stomach or in the intestine for days without producing any poisoning symptoms. However, copper can act as a poison when alloyed with other metals and reduced to a fine powdery state.
3. Copper sulphate is used often as a preservative or colouring agent to vegetables. It is also used to impart rich green colour to tinned green peas, and mango pickles. Quantity added is usually small and hence toxic effects are not produced.
4. Copper is a normal and essential constituent of human body and is found in urine, faeces, blood and other biological fluids and in liver (Normal serum level is 151.6 micrograms).
5. Suicide cases are rare.
6. Accidental poisoning results from eating food contaminated with verdigris which is formed from the action of vegetable acids on copper cooking vessels which are not properly tinned on the inside.
7. Toxicity may develop from the copper wire used in intra-uterine contraceptive devices or from the tube used in haemodialysis equipment.
8. Sometimes, the salts are taken internally for abortion.
9. Rarely it is used as a cattle poison.
10. Chronic poisoning – industrial hazard.
11. Copper sulphate was used as an antidote in phosphorus poisoning and in wound debridement.

DISCUSSION:

Acute copper poisoning is uncommon, the poisoning may be due to the accidental drinking of copper nitrate or copper sulphate solution. These and organic copper salts are strong emetics and vomiting normally rejects large doses. Chronic poisoning of copper is also very rare with few

studies relating to patients with liver disease. The ability of healthy human liver to excrete copper is considerable and it is primarily for this reason that no cases of chronic copper poisoning have been reported in individuals with healthy liver. Specific health effects of toxic compound are reported by type of health effect (systemic, immunological, reproductive, death), by route of exposure (ingestion, inhalation and skin exposure), and by length of exposure (acute, subacute, or chronic). There are many mechanisms that avoid copper overload after nutritional requirements are fulfilled. Excess copper that is absorbed into gastrointestinal mucosal cells causes synthesis and binds to the protein metallothionein. The remaining copper is transferred to the liver, where it bounds with the liver metallothionein and released into bile and excreted into the feces. While copper homeostasis plays an important role in prevention of copper toxicity. Gastro-intestinal distress is one of the most widely recorded adverse health effects of copper. It also irritates respiratory tract, copper dust exposure causes coughing, sneezing, running nose and pulmonary fibrosis. On the other hand, long term copper dust exposure can cause headaches, nausea, dizziness and diarrhea. If you drink water, containing higher amount of copper than normal you might feel nausea, vomiting and stomach cramps. Intentionally high intake of copper can damage kidneys and liver.

Toxicity of copper is a key contributor to maximum of signs, symptoms and diseases in the field of human health. It may result into number of serious and life-threatening organ dysfunction. In extreme cases of poisoning, early supportive actions are required. In addition to antidotes such as methylene blue in case of methemoglobinemia and chelating agents such as penicillamine, EDTA and BAL is designed to boost the survival of badly poisoned patients. Accurate estimates of ingestion, inhalation, skin exposures and chronic exposures are therefore needed in order to realistically access any effects of copper intakes within the general population. By recognizing how the copper imbalance occurs and how it induces metabolic dysfunction, we can prevent many of the copper induced diseases in the population. Understanding the copper toxicity is a key step to correct and to prevent most of the public health concerns.

CONCLUSION:

Close co-operation between the courts, clinical and laboratory toxicologists and forensic pathologists is essential in order to produce a correct medico-legal diagnosis of death. New legal regulations are needed to encourage a reduction in or the elimination of the use of copper products in industry, agriculture and medicine and to control the commercial availability of the compound so as to protect public health in general and to safeguard those who might consider using mercury to self-harm or to commit suicide.

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