U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Copper. [Updated 2017 Oct 30].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Copper

Updated: October 30, 2017.

OVERVIEW

Introduction

Copper is an essential trace element that is included in some over-the-counter multivitamin and mineral supplements, even though copper deficiency is quite rare and supplementation is rarely needed. The amounts of copper found in typical supplements has not been associated with serum enzyme elevations or with clinically apparent liver injury. However, accidental or intentional copper overdose can cause an acute liver injury and chronic ingestion of excessive amounts of copper can result in copper overload and chronic liver injury.

Background

Copper is a heavy metal and essential trace element that is found in many human enzymes and transcription factors. The recommended dietary allowance is approximately 1.5 mg per day. Adequate amounts of copper are found in most Western diets, with highest levels found in shellfish, chocolate and nuts. Total body copper concentrations are 50 to 120 mg (0.79 to 1.9 mmol), which is far lower than those of zinc or iron. Copper deficiency is rare and usually due to malnutrition and reduced dietary intake, but can also occur with strict vegetarian diets. Chronic oral exposure to excessive amounts of copper can result in liver injury which is also typical of Wilson disease, an inherited disease caused by a mutation in the ATPase7B gene, which encodes a hepatic enzyme responsible for the transmembrane transport and excretion of copper. The metabolic defect in Wilson disease leads to accumulation of free copper in liver and blood and secondarily in other organs, particularly brain and kidney. The disease usually presents in childhood or adolescence with neurologic syndromes, signs of advanced liver disease and hemolytic anemia. Excessive dietary intake or environmental exposure to copper is rare in the developed world, but is found in developing countries and particularly India. Nutritional supplements with copper generally have replacement doses of copper and available in many forms. Elemental copper for oral intake is not available in United States.

Hepatotoxicity

Acute hepatotoxicity of copper is usually the result of ingestion of toxic amounts (1 to 10 g), often as a suicide attempt. In children, accidental poisoning can occur, particularly with ingestion of coins. Initial symptoms may be metallic taste and gastrointestinal distress due to gastric or small bowel erosions. Acute overdoses of copper can lead to early appearance of cardiovascular collapse, coma and death within hours. Liver injury tends to arise after 24 to 72 hours and is characterized by marked elevations in serum aminotransferase levels, minimal increases in alkaline phosphatase, early appearance of hepatic failure, and elevation in prothrombin time and ensuing jaundice. Shock and renal failure may also be present as well as rhabdomyolysis and severe hemolytic anemia. The overall clinical pattern of the liver injury is that of acute hepatic necrosis, and the hepatic

manifestations resemble the acute toxicity of iron and zinc, and can be reproduced in animals. Shock and rhabdomyolysis may contribute to the serum enzyme elevations while hemolytic anemia may account for some of the increase in total bilirubin levels. Therapy of copper overdose includes gastric lavage, fluid replacement, dimercaprol (BAL) and penicillamine, with blood transfusions for hemolytic anemia and dialysis for acute renal failure.

Chronic liver injury from copper occurs with Wilson disease, but has also been described after chronic excessive ingestion of copper and perhaps as a result of chronic environmental exposure, such as from copper tubing used in hemodialysis.

Likelihood score: A[HD] (well known cause of acute and chronic liver injury but only when taken in high doses).

Drug Class: Trace Elements and Metals

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Copper Sulfate – Generic

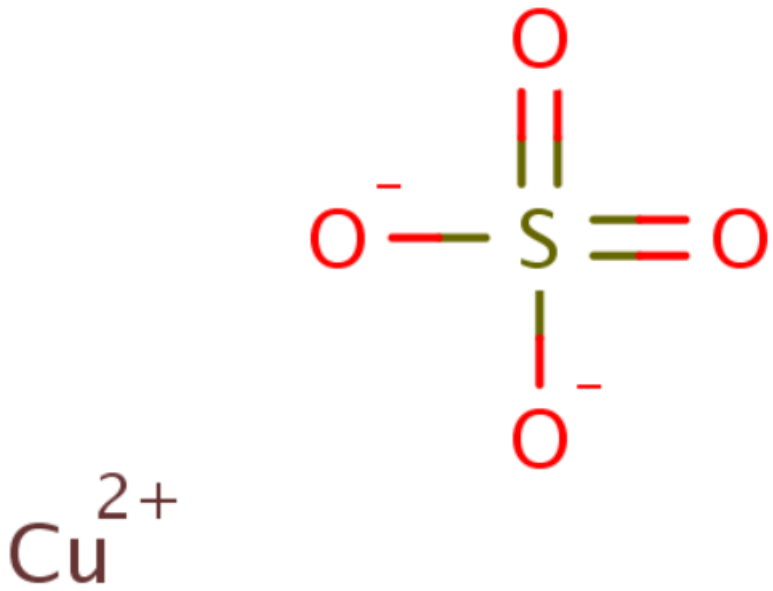
DRUG CLASS

Trace Elements and Metals

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Cupric Sulfate	7758-98-7	Cu.H2-O4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 30 October 2017

Zimmerman HJ. Copper poisoning. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, p 347.

(Review of hepatotoxicity published in 1999 mentions that copper hepatotoxicity may be acute or chronic, the acute poisoning resembling iron hepatotoxicity, the chronic injury leading to cirrhosis and possibly being the cause of Indian childhood cirrhosis).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Textbook on hepatotoxicity; the acute hepatotoxicity of copper is not discussed).

Byrns MC, Penning TM. Treatment of metal exposure. Environmental toxicology: carcinogens and heavy metals. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1872 -6.

(Textbook of pharmacology and therapeutics).

Turnlund JR. Copper. In, Shils ME, Olson JA, Shihe M, Ross AC, eds. Modern Nutrition in Health and Disease. 9th ed. Baltimore: Williams & Wilkins, 1999, pp. 241-252.

(Textbook of nutrition).

Semple AB, Parry WH, Phillips DE. Acute copper poisoning. An outbreak traced to contaminated water from a corroded geyser. Lancet 1960; 2 (7152): 700-1. PubMed PMID: 13750037.

(18 workers in a factory developed gastroenteritis after drinking tea from a single teapot contaminated with copper caused by corrosion of copper pipes; no clinical details given).

Chowdhury AK, Ghosh S, Pal D. Acute copper sulphate poisoning. J Indian Med Assoc 1961; 36: 330-6. PubMed PMID: 13693318.

(Review of 20 cases of acute copper poisoning, marked by metallic taste, epigastric pain and nausea followed by vomiting, tachycardia, hypotension and jaundice [50%] and/or hemolysis [50%]).

Gupta PS, Bhargava SP, Sharma ML. Acute copper sulphate poisoning with special reference to its management with corticosteroid therapy. J Assoc Physicians India 1962; 10: 287-92. PubMed PMID: 13903000.

(Review of 150 cases of copper poisoning seen at a single hospital in New Delhi over a 5 year period treated with gastric lavage, dimercaprol [BAL], fluids, transfusions, sedatives and corticosteroids; patient ages 13 to 60 years, 102 cases were mild and 48 severe; jaundice arising in 19%, circulatory collapse in 7% and death in 24 [16%]).

Wahl PK, Lahiri B, Mathur KS, Kehar U, Wahi PN. Acute copper sulphate poisoning. J Assoc Physicians India 1963; 11: 93-103. PubMed PMID: 13998300.

(Review of 50 cases of copper poisoning admitted over a 2 year period to a single hospital in India, treated with gastric lavage, dimercaprol [BAL] and fluids, 17 patients [34%] developing jaundice, arising between days 2 and 5, ALT ranging from 30 to 150 U/L and autopsy in 7 showing focal necrosis and fatty change in the liver).

Chuttani HK, Gupta PS, Gulati S, Gupta DN. Acute copper sulfate poisoning. Am J Med 1965; 39: 849-54. PubMed PMID: 5833579.

(Description of 53 patients with acute copper poisoning, ages 14 to 60 years, 32 men and 21 women, usually with suicidal intent, presenting with metallic taste, nausea, vomiting and epigastric burning, jaundice arising in 23%, usually on days 2 or 3, leading to death in some or resolving in 2-5 days, liver showing centrilobular necrosis and cholestasis).

Fairbanks VF. Copper sulfate-induced hemolytic anemia. Inhibition of glucose-6-phosphate dehydrogenase and other possible etiologic mechanisms. Arch Intern Med 1967; 120: 428-32. PubMed PMID: 4293707.

(22 year old woman had accidental ingestion of copper sulfate and developed nausea, vomiting and diarrhea for 2 days followed by dark urine and hemolysis [hematocrit falling to 20%], with slow recovery; all liver tests were normal).

Singh MM, Singh G. Biochemical changes in blood in cases of acute copper sulphate poisoning. J Indian Med Assoc 1968; 50: 549-54. PubMed PMID: 5708633.

(Among 40 patients with acute copper poisoning, 27 were men, 13 women, ages 13 to 85 years, AST levels ranged from 36-3400 U/L, ALT 66-440 U/L, bilirubin 0.4-30 mg/dL [most less than 2.0 mg/dL] and 4 patients died, one of hepatic failure and three from hemolysis).

Deodhar LP, Deshpande CK. Acute copper sulphate poisoning. J Postgrad Med 1968; 14: 38-41. PubMed PMID: 5648509.

(Seven autopsied cases of acute copper intoxication, included 5 who died within hours of presentation and 2 on day 5 with jaundice [bilirubin 7.0 and 7.7 mg/dL] and "cloudy and fatty degeneration of liver cells", with focal and centrilobular necrosis).

Papadoyanakis N, Katsilambros N, Patsourakos B. Acute copper sulfate poisoning with jaundice. J Ir Med Assoc 1969; 62: 99-100. PubMed PMID: 5776964.

(36 year old man took and overdose of copper sulfate and was admitted in coma three hours later and developed hemolytic anemia and jaundice the following day [bilirubin rising to 6.6 mg/dL, AST 190 U/L], dying 11 days after ingestion and autopsy showing cholestasis and inflammation, but "necrosis was not seen").

Manzler AD, Schreiner AW. Copper-induced acute hemolytic anemia. A new complication of hemodialysis. Ann Intern Med 1970; 73: 409-12. PubMed PMID: 5455992.

(3 men developed copper intoxication during hemodialysis with acute onset of nausea, diarrhea and lethargy and acute hemolysis; no mention of liver test abnormalities).

Chugh KS, Singhal PC, Sharma BK. Letter: Methemoglobinemia in acute copper sulfate poisoning. Ann Intern Med 1975; 82: 226-7. PubMed PMID: 1115446.

(27 year old man took an overdose of copper sulfate which led to vomiting and lethargy followed by cyanosis, oliguria, methemoglobinemia, intravascular hemolysis, shock and death 16 hours after the ingestion).

Klein WJ Jr, Metz EN, Price AR. Acute copper intoxication. A hazard of hemodialysis. Arch Intern Med 1972; 129: 578-82. PubMed PMID: 5019446.

(Hemodialysis using copper tubing can result in significant copper exposure; 3 adults, ages 35 to 53 years, developed headache, myalgias, fatigue, diarrhea and nausea during hemodialysis with severe hemolytic anemia, metabolic acidosis, high serum copper levels, progressive coma and death, sometimes with minor AST and bilirubin elevations).

Agarwal BN, Bray SH, Bercz P, Plotzker R, Labovitz E. Ineffectiveness of hemodialysis in copper sulphate poisoning. Nephron 1975; 15: 74-7. PubMed PMID: 1128758.

(41 year old woman took an overdose of copper sulfate developing vomiting and diarrhea, and was treated with fluids, EDTA, gastric lavage and hemodialysis, but had progressive hemolysis and liver and renal failure [bilirubin 0.6 mg initially rising to 20.6 mg/dL, AST to >6000 U/L, Alk P 139 U/L, LDH 8,500 U/L, CPK 4,100 U/L], dying after 5 days).

Stein RS, Jenkins D, Korns ME. Letter: Death after use of cupric sulfate as emetic. JAMA 1976; 235: 801. PubMed PMID: 946302.

(44 year old woman with a three-quarter gastrectomy was given cupric sulfate as an emetic after an overdose of diazepam and developed lethargy and hypotension one hour later, followed by severe hemolytic anemia, respiratory, hepatic and renal failure, dying 6 days later).

Walsh FM, Crosson FJ, Bayley M, McReynolds J, Pearson BJ. Acute copper intoxication. Pathophysiology and therapy with a case report. Am J Dis Child 1977; 131: 149-51. PubMed PMID: 835530.

(18 month old boy drank a copper sulfate solution and developed nausea, vomiting and lethargy, high serum copper [1,650 µg/dL] and hemolysis, responding to dimercaprol [BAL] treatment with resolution within one week, liver tests remaining normal).

Chugh KS, Sharma BK, Singhal PC, Das KC, Datta BN. Acute renal failure following copper sulphate intoxication. Postgrad Med J 1977; 53: 18-23. PubMed PMID: 876909.

(Among 29 patients with acute copper poisoning admitted to a referral hospital in India over a 10 year period, 11 [38%] presented with acute renal failure, usually after 3-8 days [creatinine 2.5-14.5 mg/dL] and liver injury [27%] [bilirubin 1.5-14.5 mg/dL, serum copper 115-8269 µg/dL, hemoglobin 2-9 g/dL]).

Chugh KS, Sakhuja V. Acute copper intoxication. Int J Artif Organs 1979; 2: 181-2. PubMed PMID: 457302.

(Brief review of the clinical manifestations and management of acute copper intoxication).

Sternlieb I. Copper and the liver. Gastroenterology 1980; 78: 1615-28. PubMed PMID: 6245986.

(Review of the metabolism of copper and its role in Wilson disease).

Schwartz E, Schmidt E. Refractory shock secondary to copper sulfate ingestion. Ann Emerg Med 1986; 15: 952-4. PubMed PMID: 3740585.

(62 year old man took an overdose of copper sulfate and developed nausea, vomiting and stupor with persistent hypotension followed by severe hemolytic anemia and elevated liver enzymes and death, no details of liver tests provided).

Yelin G, Taff ML, Sadowski GE. Copper toxicity following massive ingestion of coins. Am J Forensic Med Pathol 1987; 8: 78-85. PubMed PMID: 3578211.

(58 year old woman with severe neuropsychiatric disability, developed nausea, weight loss, jaundice and stupor [bilirubin 11.7 mg/dL, direct bilirubin 7.0 mg/dL, ALT 53 U/L, Alk P 2.2 U/L, pH 6.86, lactate 30.9 mg/dL, hemoglobin 4.6 g/dL, reticulocyte count >20%] and died in coma 38 hours later, autopsy showing 275 coins in stomach and liver with fat, Mallory bodies, fibrosis and excess copper).

Mueller PD, Benowitz NL. Toxicologic causes of acute abdominal disorders. Emerg Med Clin North Am 1989; 7: 667-82. PubMed PMID: 2663462.

(Review of gastrointestinal toxicity of agents including iron, mercury and copper).

Hantson P, Lievens M, Mahieu P. Accidental ingestion of a zinc and copper sulfate preparation. J Toxicol Clin Toxicol 1996; 34: 725-30. PubMed PMID: 8941204.

(86 year old woman inadvertently drank a zinc and copper sulfate solution, rapidly developed vomiting and watery diarrhea [copper 209 µg/dL, normal <140: zinc 1979 µg/dL, normal <123], was treated with gastric lavage, hydration, penicillamine and dimercaprol [BAL], but developed hypotension, respiratory and renal failure, while liver tests remained normal; she ultimately recovered).

Strubelt O, Kremer J, Tilse A, Keogh J, Pentz R, Younes M. Comparative studies on the toxicity of mercury, cadmium, and copper toward the isolated perfused rat liver. J Toxicol Environ Health 1996; 47: 267-83. PubMed PMID: 8604150.

(Comparison of toxicity of equimolar amounts of mercury, cadmium and copper in an isolated, perfused rat liver system found similar patterns of toxicity which appeared to be mitochondrial with reductions in ATP levels).

Bennett DR, Baird CJ, Chan KM, Crookes PF, Bremner CG, Gottlieb MM, Naritoku WY. Zinc toxicity following massive coin ingestion. Am J Forensic Med Pathol 1997; 18: 148-53. PubMed PMID: 9185931.

(55 year old man with schizophrenia developed nausea, anorexia, epigastric pain and gastrointestinal bleeding, and ultimately was found to have 461 coins in the stomach which were removed surgically, but he developed renal and hepatic failure [peak bilirubin 12.2 mg/dL, ALT 341 U/L, AST 1141 U/L], autopsy showing massive hepatic and acute tubular necrosis).

Rodeck B, Kardoff R, Melter M. Treatment of copper associated liver disease in childhood. Eur J Med Res 1999; 4: 253-6. PubMed PMID: 10383883.

(Two German children, ages 6 and 10 months, developed abdominal swelling and ascites [bilirubin 3.0 and 8.8 mg/dL, ALT 325 and 170 U/L, GGT 140 U/L], high copper levels found in liver and in well water, one improved with penicillamine therapy, but the second required liver transplantation).

Takeda T, Yukioka T, Shimazaki S. Cupric sulfate intoxication with rhabdomyolysis, treated with chelating agents and blood purification. Intern Med 2000; 39: 253-5. PubMed PMID: 10772131.

(18 year old man took an overdose of cupric sulfate and developed vomiting and lethargy [serum copper 142 µg/dL, normal <131], was treated with gastric lavage, penicillamine and dimercaprol [BAL], but developed myoglobinemia, hemolysis and rhabdomyolysis [peak CK 3,804 U/L on day 6] with mild renal and liver injury, ultimately resolving after 18 days).

Dietrich AM, Glindemann D, Pizarro F, Gidi V, Olivares M, Araya M, Camper A, et al. Health and aesthetic impacts of copper corrosion on drinking water. Water Sci Technol 2004; 49(2): 55-62. PubMed PMID: 14982164.

(Corrosion of copper pipes can cause excess copper in the water supply that is associated with metallic taste and increase in gastrointestinal illness).

Srivastava A, Peshin SS, Kaleekal T, Gupta SK. An epidemiological study of poisoning cases reported to the National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi. Hum Exp Toxicol 2005; 24: 279-85. PubMed PMID: 16004194.

(Among 2719 calls to an Indian poisoning center over a 3 year period, 48 [2%] were concerning copper sulfate).

Donoso A, Cruces P, Camacho J, Rí JC, Paris E, Mieres JJ. Acute respiratory distress syndrome resulting from inhalation of powdered copper. Clin Toxicol (Phila) 2007; 45: 714-6. PubMed PMID: 17849249.

(2 year old girl spilled copper powder on her face and inhaled some of the contents, developing cough, dyspnea and cyanosis and, on admission, had hypoxia and acidosis, developing respiratory and renal failure and evidence of liver injury over the next several days [AST 105 U/L, ammonia 120 µmol/L, prothrombin index 20%], but ultimately recovered).

Franchitto N, Gandia-Mailly P, Georges B, Galinier A, Telmon N, DucasséL, Rougé. Acute copper sulphate poisoning: a case report and literature review. Resuscitation 2008; 78: 92-6. PubMed PMID: 18482790.

(29 year old man developed vomiting and diarrhea shortly after taking overdose of copper sulfate [homemade rat poison], with fever and acute psychosis, initially with normal liver and renal tests, developing mild hemolytic anemia and renal dysfunction, treated with EDTA and dimercaprol [BAL], and resolving within 1 week).

Hassan S, Shaikh MU, Ali N, Riaz M. Copper sulphate toxicity in a young male complicated by methemoglobinemia, rhabdomyolysis and renal failure. J Coll Physicians Surg Pak 2010; 20 (7): 490-1. PubMed PMID: 20642956.

(22 year old man accidentally drank a cup of copper sulfate and developed severe vomiting, abdominal pain and dehydration, treated with gastric lavage, penicillamine and dimercaprol [BAL], with increase in methemoglobinemia, acute renal failure, liver dysfunction [bilirubin 2.9 mg/dL, ALT 85 U/L, Alk P 30 U/L] and adult respiratory distress syndrome, eventually improving and resolving within 2 weeks).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to ingestion of copper).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(Among 313 cases of drug induced liver injury seen between 1997 and 2008 at a large hospital in Bangalore, India, none were attributed to copper ingestion or copper overdoses).

Valsami S, Stamoulis K, Lydataki E, Fountoulaki-Paparizos L. Acute copper sulphate poisoning: a forgotten cause of severe intravascular haemolysis. Br J Haematol 2012; 156: 294. PubMed PMID: 21981599.

(25 year old man presented 18 hours after overdose with copper sulfate with hemolytic anemia [hematocrit initially 44% falling to 25% in 3 days], with rhabdomyolysis and mild renal and liver impairment).

Naha K, Saravu K, Shastry BA. Blue vitriol poisoning: a 10-year experience in a tertiary care hospital. Clin Toxicol (Phila) 2012; 50: 197-201. PubMed PMID: 22372787.

(Among 35 cases of acute copper poisoning presenting at a single referral center in Southern India over a 10 year period, the average age was 29 years, symptoms included vomiting [85%], diarrhea [46%], epigastric pain [43%], blood in stool [31%), hematuria [26%], burning chest pain [17%] and jaundice [37%] and 8 patients died).

Weiss KH, Stremmel W. Evolving perspectives in Wilson disease diagnosis: treatment and monitoring. Curr Gastroenterol Rep 2012; 14: 1-7. PubMed PMID: 22083169.

(Review of the diagnosis and management of Wilson disease, including the role of genetic testing and the choice of medical therapies).

Rifkin J, Miller MD. Copper-associated hepatitis in a Pembroke Welsh corgi. Can Vet J 2014; 55: 573-6. PubMed PMID: 24891642.

(6 year old Welsh corgi developed poor appetite and weight loss and was found to have liver injury [bilirubin not given, ALT 1366 U/L, Alk P 201 U/L], laparotomy showing an abnormal looking liver with fatty change, fibrosis and excessive copper, later responding to penicillamine, ursodiol andS-adenosylvmethionine with normalization of ALT levels).

Breuer C, Oh J, Nolkemper D, Achilles EG, Fischer L, Eglite I, Guesmer C, et al. Successful detoxification and liver transplantation in a severe poisoning with a chemical wood preservative containing chromium, copper, and arsenic. Transplantation 2015; 99: e29-30. PubMed PMID: 25827325.

(4 year old boy ingested wood preservative with chromated copper arsenate and rapidly developed abdominal pain and vomiting followed by acute liver and kidney failure treated with dialysis, BAL and liver transplantation 5 days later; liver showing "toxic liver damage").

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none of the cases were attributed to copper ingestion).