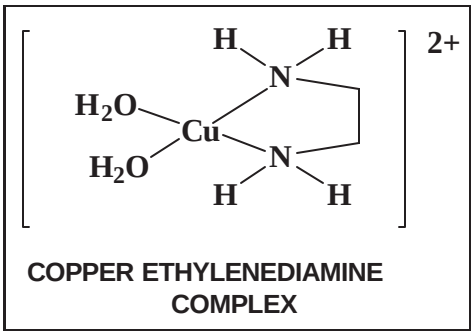
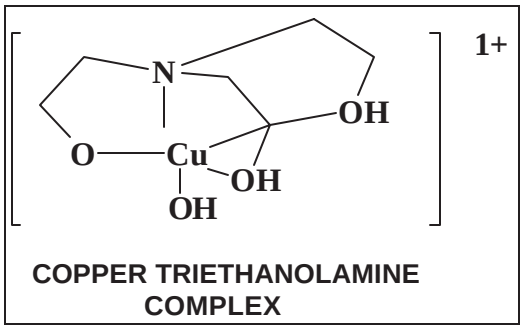
III.1 COPPER and COPPER COMPLEXES





SUMMARY

Copper is an element used as an aquatic herbicide in several different formulations. All products have been used to control algae and other aquatic vegetation in slow-moving or quiescent bodies of water including golf courses, ornamental fish and irrigation ponds, lakes and rivers (WSSA, 1994).

Copper is naturally occurring and is found in soil and water often in the form of complexes, both organic and inorganic. Removal of elemental copper from an aqueous system occurs through binding to sediments and dissolved organic compounds.

Copper is an essential element in humans, animals and plants, but in high enough concentrations it can be harmful to biota. Toxicity of copper is related to water hardness; copper in water with a hardness of less than 20 mg/l $CaCO_3$ is more toxic to fish than copper in the water at a greater hardness.

Copper complexes have been developed that serve to decrease the availability of the copper ion in the water column through chelation. Ionic copper in solution normally complexes with carbonates. The chelated copper complexes prevent these copper carbonates from forming, thereby decreasing the toxicity to non-target organisms including humans and fish (Ross and Lembi, 1985). Four chemical formulations of copper discussed in this report include copper sulfate, a mixed ethanolamine complexan ethylene diamine complex) and a triethanolamine complex. There is little information available for the formulated products of copper primarily because the USEPA only recently began requiring toxicity and environmental fate and persistence data on these products (Orr, pers. comm., 1995). These formulations contain varying percentages of copper along with a variety of proprietary inert ingredients. Data on the copper ion, considered to be the active ingredient in all of the formulations, are available.

The copper ion (copper II) is responsible for the toxicity of all of the formulations. Although the mechanism has not unequivocally been elucidated, it is believed that high levels of copper interfere with photosynthesis. Inhibition of photosynthesis leads to plant death.

REGISTERED PRODUCTS IN MASSACHUSETTS

The current list of aquatic herbicides containing copper that are registered in Massachusetts can be accessed at http://www.state.ma.us/dfa/pesticides/water/Aquatic/Herbicides.htm on the Massachusetts Department of Agricultural Resources (DAR) Aquatic Pesticide Website. The DAR updates this list regularly with changes. In addition, the DAR can be contacted directly at (617) 626-1700 for more specific questions regarding these products.

COPPER AND COMPLEXES USES AND APPLICATIONS

Copper and chelated copper complexes are used to control the growth of algae and other aquatic vegetation that are considered a nuisance. The carbonate activity of the water in which it is found greatly influences copper sulfate activity. Copper sulfate ionizes in water. The ionic copper forms complexes with carbonates which precipitate out of solution. Carbonate concentration (or hardness) is directly related to alkalinity. Thus, in harder, more alkaline waters the copper rapidly precipitates out of solution which reduces the toxicity to algae. Alternatively, in more acidic, softer waters most of the copper stays in solution for a longer period of time. Thus, copper sulfate is generally more effective in soft water (although it is also more toxic to fish in soft water). Chelated copper complexes prevent the precipitation of copper from solution and therefore are longer lasting, particularly in harder, alkaline waters (Ross and Lembi, 1985).

Copper sulfate is used primarily to control algal growths in impounded waters, lakes, ponds, reservoirs and irrigation and irrigation drainage conveyance systems. In impounded waters, copper sulfate can be applied by spraying the water surface from a boat. Finer crystals can be dusted on the water surface. Large crystals can be put into a burlap bag and towed behind a boat. In irrigation conveyance systems, large or granular crystals are dumped into the ditch at required dosages at intervals, or for pondweed control, finer crystals are continuously metered into the flowing water by a specially designed feeder.

For specific information on recommended application rates for a particular product, the product label should be consulted. The USEPA Office of Pesticide Programs (OPP) has a link to a database of product pesticide labels at http://www.epa.gov/pesticides/pestlabels/.

MECHANISM OF ACTION

High levels of copper inhibit the growth of algae and other plants by causing an imbalance in cofactors involved with enzyme function, especially those involved with photosynthesis. Inhibition of photosynthesis leads to a diminished ability to thrive and eventually to plant death (WSSA, 1994).

ENVIRONMENTAL FATE/TRANSPORT

The environmental fate and persistence of copper is dependent upon how it is distributed in the environment. Copper occurs naturally in the aqueous environment in the +1 oxidation state, also called the cuprous ion and in the +2 oxidation state, also called the cupric ion (WSDOE, 1992). The +3 oxidation state is uncommon and found only in the solid state. Copper is a transition metal which means it has the ability to form coordination complexes with a number of ligands including clays and humic substances, the amine and sulfhydryl groups of proteins, ethanolamines and ethylene diamine (EDA). These complexes are highly water soluble (WSSA, 1983) and largely of low toxicity (USEPA, 1980). The amount of copper that is bound to these compounds is dependent on the pH, metal concentration and the humic content of the water. Table III.1-2 (at the end of the copper section) lists selected

physicochemical characteristics of formulations of copper sulfate, copper ethylene diamine complexes, copper triethanolamine complexes and copper ethanolamine complexes.

Since copper is an element, biodegradation does not occur in aquatic ecosystems. Copper in aquatic ecosystems can be present in soluble form or it may be associated with particles in such ways as sorption, chelation, co-precipitation and biological accumulation by plankton. Removal from an aqueous phase occurs primarily through the adsorption of copper to sediments and is therefore not removed from the environment (WSSA, 1983). Copper can remain in the environment indefinitely if it is not physically removed. Types and kinds of organic matter in an aqueous system are important determinants of the free copper concentrations (WSDOE, 1992). Dissolved aqueous copper half-lives were reported from studies done in six Manitoba lakes (Wageman and Barica, 1979). In five of the six lakes the half-lives were between 1 and 2 days. In the other lake the half-life was 7 days.

Copper bioconcentrates in some aquatic organisms as shown in Table III.1-1.

Table III.1-1. Copper Bioconcentration Factors for Several Aquatic Species

ORGANISM	BCF
Hard shell clam (*Mercinaria mercinaria*)	88[1]
Green alga (*Chlorella vulgaris*)	2,000[1]
Fathead minnow (*Pimephales promelas*)	290[1]
Water flea (*Daphnia magna*)	1200 to 7100[2]

1 USEPA, 1980
2 Winner, 1985

PHARMACOKINETICS

Absorption of ingested copper occurs mainly in the upper portion of the gastrointestinal tract, with appearance of copper bound to albumen and amino acids in the blood within 1-2 hours of administration. The absorbed copper accumulates in the liver reducing blood copper levels. Blood copper levels then begin to rise slowly as a result of the hepatic production and release of copper-bound ceruloplasmin. Copper is also incorporated into several other proteins including the enzymes cytochrome oxidase, monoamine oxidase, tyrosinase and erythrocyte superoxide dismutase. Low molecular weight copper complexes are excreted rapidly with increasing amounts of high molecular weight copper complexes being formed over time. Copper elimination occurs primarily by the fecal route with relatively little excreted through urine, sweat or menstrual fluid (USEPA, 1987).

HEALTH EFFECTS

Mammalian:

While limited information on the pharmacokinetics and health effects of elemental copper exists, there is very little information on these subjects for the copper complexes. Since copper is considered to be the active component of the copper complexes, a summary of the toxicity of elemental copper is presented here.

Copper

Copper is an essential element in humans and other animals therefore most of the adverse health effects associated with copper are a result of its deficiency. Efficient homeostatic mechanisms generally protect mammals from the adverse effects of copper excess (USEPA, 1987). Copper is a component of enzymes that are vital in hematopoiesis, maintenance of vascular and cellular integrity and structure and function of the central nervous system (O'Dell, 1976 as cited in USEPA, 1987). Several enzymes use copper as a coenzyme including tyrosinase, cytochrome oxidase, superoxide dismutase and amine oxidase. Menke's disease and Wilson's disease are two genetic diseases associated with the increased sequestration of copper in brain and other tissues. Infants and children have increased susceptibility to the toxic effects of copper probably because of the normally high hepatic copper levels in early life and the fact that homeostatic mechanisms are not fully developed at birth.

Acute:

Thirteen of 53 patients died after ingesting 6-637 mg/kg copper in attempted suicides. These doses are much higher than doses from ingestion of water containing copper applied at recommended label application rates. Cause of death was reported to be shock and liver and/or kidney complications (Chuttani *et al.*, 1965 as cited in USDHHS, 1990). Increased mortality was reported in rats fed 4,000 ppm of copper for 1 week (Boyden *et al.*, 1938 as cited in USDHHS, 1990) and in weanling rats exposed to 6,000 ppm for 2 weeks (Haywood, 1985 as cited in USDHHS, 1990). The deaths were attributed to liver effects (i.e., centrilobular necrosis). Acute systemic effects observed upon consumption of contaminated water or copper sulfate in attempted suicides include gastrointestinal, liver and kidney effects (USDHHS, 1990). In animals, in addition to the ones noted in humans, effects on the blood, musculoskeletal and cardiovascular systems were also noted as well as changes in body weight (USDHHS, 1990).

Subchronic/Chronic:

Copper produces liver damage as the liver is the main storage depot for copper. The specific mechanism of liver toxicity has not been elucidated, but administration of copper compounds to laboratory animals has resulted in hepatocellular necrosis, regenerative activity, cirrhosis, Kupffer cell mobilization and hepatocellular pigment formation (Barka *et al.*, 1964 as cited in USEPA, 1987). Excessive subchronic ingestion of copper also produced kidney damage in rats (Rana and Kumar, 1980; Haywood, 1980 as cited in USEPA, 1987) but this only occurred after the liver began to accumulate high levels of copper (Haywood, 1980 as cited in USEPA, 1987). Blood levels of copper rise after copper accumulates in the liver.

There are few chronic copper toxicity studies available (except for in ruminant animals) and those that are available are characterized by serious experimental flaws (USDHHS, 1990). Ingestion of 150 mg copper/kg/day (i.e., 500 ppm dietary copper) by rats for 1 week resulted in no observable effects (e.g., no liver accumulation and no adverse kidney or liver changes). Administration of this dose to rats for six weeks caused severe kidney and liver damage in rats. Continued administration of this dose for up to 15 weeks resulted in no further damage but instead produced a regeneration of liver and kidney tissues (Haywood, 1980 as cited in USEPA, 1987). Liver and kidney necrosis occurred in rats fed 25.4 mg copper/kg/day for 20 days (Rana and Kumar, 1980 as cited in USEPA, 1987).

In rats fed 500 ppm copper in the diet for 27 days (Boyden, et al, 1938 as cited in USEPA, 1987) and 50 ppm copper for 35 days (Miranda *et al.*, 1981 as cited in USEPA, 1987), increased liver copper concentrations were noted. Higher levels resulted elevated copper levels in the liver and spleen, growth reduction and reduced dietary intake, resulting in death (Boyden *et al.*, 1938 as cited in USEPA, 1987).

Adverse effects were reported in pigs given copper supplements of 600 ppm in the diet for 48 days and 250 ppm for 79 days (Kline *et al.*, 1971 as cited in USEPA, 1987) whereas beneficial effects were reported in pigs dosed with 150-200 ppm for 61-88 days. A dose of 500 ppm administered in the diet for 61 days caused adverse effects including growth reduction, reduced hemoglobin and increased hepatic copper (Kline *et al.*, 1971 as cited in USEPA, 1987).

Developmental/Reproductive:

Copper compounds produced teratogenic effects at approximately 2 mg copper/kg when injected into female hamsters on the eighth day of pregnancy (DiCarlo, 1980; Ferm and Hanlon, 1974 as cited in USEPA, 1987); however, injection is not a normal route of exposure so these results do not provide any conclusive information on effects via oral exposures. In mice fed greater than 104 mg copper/kg/day as copper sulfate, increased fetal mortality was observed; developmental abnormalities were observed at greater than 155 mg copper/kg/day (Lecyk, 1980 as cited in USDHHS, 1990). In mink administered dietary copper sulfate levels greater than 3 mg copper/kg/day, an increased mortality rate in offspring was noted. 3 mg/kg/day was identified as the LOAEL for developmental effects in mink (Aulerich, *et al.*, 1982 as cited in USDHHS, 1990). A significant increase in testes weight was observed in rats treated with 130 mg copper/kg/day as copper acetate administered via the diet (Llewellyn *et al.*, 1985 as cited in USDHHS, 1990). A NOAEL of 13 mg/kg/day for reproductive effects was reported for mink (Aulerich *et al.*, 1982 as cited in USDHHS, 1990).

Mutagenicity:

Copper was generally found to produce negative results in microbial mutation assays. Low concentrations of copper have produced some mutagenic activity in cell culture assays. Copper sulfate produced an increase in the frequency of recessive lethal mutations in *D. melanogaster* at high concentrations (Law, 1938 as cited in USEPA, 1987).

Carcinogenicity:

Limited information available on the carcinogenicity of copper is equivocal. Tumors were induced in mice administered copper by subcutaneous injection (BRL,1968 as cited in USEPA, 1987). Copper-induced cancer was not reported to occur in rats or mice exposed to copper at dietary concentrations ranging from 5-1,000 mg/kg/day (Greene *et al.*, 1987, Kamamoto *et al.*, 1973 as cited in USDHHS, 1990). Based on the limited information, the U.S. EPA Office of Pesticide Programs (OPP) has designated copper as a Group E carcinogen under the old EPA cancer classification system. Under the new EPA classification system using descriptors, this classification corresponds to a descriptor of "Data are inadequate for the assessment of human carcinogenic assessment".

Other Information on Specific Copper Compounds:

Copper Sulfate

The toxic properties of copper sulfate are mainly attributable to its caustic properties (NRC, 1977). Symptoms of acute copper toxicity include metallic taste in the mouth, burning epigastric pain, vomiting, diarrhea, nausea and depending on the severity, jaundice, hemolysis, blood and urine effects. In severe cases, anuria, hypotension and coma can occur (USEPA, 1980). Skin contact with copper sulfate results in eczema; contact with the eyes causes conjunctivitis, edema of the eyelids, and ulceration and turbidity of the cornea (Patty, 1963). One infant fatality was reported following exposure to copper sulfate at a concentration of 6.75 mg/l in drinking water for 14 months (NRC, 1977).

Copper Ethanolamine Complexes

The acute oral LD50 in rats for a formulation of copper ethanolamine complexes has been reported to be between 650 and 2420 mg/kg (Applied Biochemists, 1994; WSSA, 1994). An oral LD50 has been reported in rats of 498 mg/kg. In rabbits, the acute dermal LD50 is greater than 2,000 mg/kg (WSSA, 1994).

Copper Triethanolamine Complexes

In an acute inhalation study done in Sprague-Dawley rats exposed to a formulation of copper triethanolamine complexes, LC50 values of 0.27 mg/l for male rats and 1.15 mg/l for female rats were derived (Griffin Corporation, 1992). An oral LD50 of 1200-2400 mg/kg and a dermal LD50 of 9600 mg/kg were reported in rabbits (WARF Institute, 1972; WSSA, 1994).

Available Toxicity Criteria:

The Environmental Protection Agency (EPA) has developed a health-based Maximum Contaminant Level Goal (MCLG) of 1.3 mg/l for copper in drinking water. The EPA determined that it would not be feasible to set a Maximum Contaminant Level (MCL) standard for copper and therefore they established an Action Level of 1.3 mg/l accompanied by a treatment approach involving corrosion control, source water reduction, public education and copper service line replacement designed to achieve the public health goals of the Safe Drinking Water Act. The EPA also established a secondary MCL of 1 mg/l based on odor and taste considerations of drinking water (USEPA, 1992).

ECOLOGICAL TOXICITY

Aquatic Organisms :

Invertebrates:

The toxicity of copper to aquatic invertebrates generally decreases as hardness increases. Additional data for several species indicate that toxicity also decreases with increases in alkalinity and total organic carbon (USEPA AWQC, 1980). There is a wide range of acute toxicity responses (LC50, EC50) for invertebrates. Concentrations for crustaceans ranged from 5 to 300 µg/l; for annelids, the range was from 6 to 900 µg/l; and for mollusks the range was 40 to 9,000 µg/l (WSDOE, 1992). In another study, acute LC50 values ranged from less than 10 to 9,000 µg/l in crustaceans and from 39 to 2600 µg/l in mollusks (Harrison, 1985).

There is a large body of data for the fresh water crustacean *Daphnia* spp. In four species of *Daphnia*, LC50 values ranged from 68 to 87 µg/l (Speara and Pierce cited in Harrison, 1986). *D. magna* are capable of developing tolerance to copper but *D. pulex* are not (LeBlanc, 1985 in Harrison, 1986). However, *D. pulex* can be sensitized to copper toxicity (LeBlanc, 1985).

Four species of *Daphnia* experienced decreased survivorship when exposed to 0.040 mg/l of copper under laboratory conditions using a static method with water at 100-119 mg/l alkalinity, 130-160 mg/l hardness and 8.2-9.5 mg/l of dissolved oxygen (WSDOE, 1992). In a continuous flow bioassay (41 mg/l hardness, pH 7.7 and 43 mg/l alkalinity), the survival of the snail (*Physa integra*), amphipod (*Gammarus pseudolineus*) and operculate snail (*Campeloma decisum*), was reduced at 0.0148 and 0.028 mg/l copper (Arthur and Leonard, 1970). No growth inhibition was observed at 0.008 mg/l or less.

Vertebrates:

The copper (II) ion is believed to be the toxic form of copper to fish (WSDOE, 1992). The amount of the copper (II) form is dependent upon pH and therefore copper toxicity is related to pH (Chapman, 1977).

In addition, several studies have demonstrated that copper toxicity is related to water hardness. In water with a hardness of approximately 20 mg/l (as calcium carbonate), copper concentrations of 0.040 mg/l are reported to be toxic to salmonid eggs, fry, fingerling, juveniles and adults (Chu *et al.*, 1978). Fish tested in water with concentrations of $CaCO_3$ greater than 20 mg/l (harder water) were less sensitive.

There are several studies available that characterize toxicity of copper to fish. Large differences are seen in the sensitivities of different species to copper. Acute toxicity (48h to 96h LC50 or EC50) data for freshwater fishes range from 10-900 µg/l for Salmonidae, 700-110,000 µg/l for Centrarchidae and 20-2,000 µg/l for Cyprinidae (WSDOE, 1992).

In bluegill sunfish, LC50 values for a formulation of copper triethanolamine complexes ranged from 1.2 mg/l in soft water to 7.5 mg/l in hard water. In channel catfish the 96 hour LC50 value of 6 mg/l has been reported. The 96 hour LC50 value for rainbow trout is less than 0.2 mg/l in soft water and 4 mg/l in hard water (WSSA, 1994). Specific toxicity information for copper triethanolamine formulations was not found.

Death in fish from acute exposures may be due to the disruption of the respiratory process caused by damage to the gill epithelium. The effects of copper sulfate and copper nitrate were studied in the chinook salmon (Holland *et al.*, 1960). At concentrations of 0.178 to 0.318 mg/l between 42 and 96 hours, fifty percent mortality was reported. Total kills occurred in 18 hours when fish were exposed to 1 mg/l of copper and in less than 42 hours at concentrations of 0.563 mg/l.

Available Toxicity Criteria:

The EPA has developed a number of Ambient Water Quality Criteria (AWQC) for copper for both acute and chronic exposures of both freshwater and marine organisms. These include freshwater and marine acute values of 9.2 µg/l and 2.9 µg/l respectively as well as a freshwater chronic value of 6.5 µg/l (USEPA, 1992). (All of the AWQC values are dependent on the hardness of the water.)

Plants:

Copper has been used to control nuisance vegetation for many years. Concentrations of copper of 1-2 µg/l inhibit photosynthesis and plant growth (WSDOE, 1992). Toxicity data for individual plant species are lacking (USEPA, 1980).

The effects of pH on the toxicity of copper to algae can be important. Laboratory results demonstrated that changes in metal toxicity with pH resulted from competition between the hydrogen ion and the copper II ion for cellular binding sites at the lower pH range. At higher pH copper was still toxic because of the decreased competition of the hydrogen ion (WSDOE, 1992).

Table III.1-2. Physicochemical Properties of Formulations of Various Copper Compounds

Parameter	Copper Sulfate	Copper Ethylene Diamine Complex[1]	Copper Triethanolamine Complexes[2]	Mixture of Copper Carbonate, Monoethanolamine and Triethanolamine
Molecular Formula	$CuSO_4$	$C_2H_{12}CuN_2O_2$	$C_6H_{15}CuNO_4$	Proprietary
Molecular Weight (g/mol)	161.39	255.73	228.74	n/a
Density (mg/l)	2.28 (Sax)	1.22	1.20	1.1-1.3
Boiling Point (degrees C)	n/a	102	n/a	212
Water Solubility	completely miscible	completely miscible	completely miscible	completely miscible

n/a not applicable

1. WSSA, 1994.
2. Applied Biochemists, 1995.

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