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COPPER AND COPPER-CONTAINING PESTICIDES: METABOLISM, TOXICITY AND OXIDATIVE STRESS

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Abstract. The purpose of this paper is to provide a brief review of the current knowledge regarding metabolism and toxicity of copper and copper-based pesticides in living organisms. Copper is an essential trace element in all living organisms (bacteria, fungi, plants, and animals), because it participates in different metabolic processes and maintain functions of organisms. The transport and metabolism of copper in living organisms is currently the subject of many studies. Copper is absorbed, transported, distributed, stored, and excreted in the body via the complex of homeostatic processes, which provide organisms with a needed constant level of this micronutrient and avoid excessive amounts. Many aspects of copper homeostasis were studied at the molecular level. Copper based-pesticides, in particularly fungicides, bacteriocides and herbicides, are widely used in agricultural practice throughout the world. Copper is an integral part of antioxidant enzymes, particularly copper-zinc superoxide dismutase (Cu,Zn-SOD), and plays prominent roles in iron homeostasis. On the other hand, excess of copper in organism has deleterious effect, because it stimulates free radical production in the cell, induces lipid peroxidation, and disturbs the total antioxidant capacity of the body. The mechanisms of copper toxicity are discussed in this review also.

Keywords: copper, copper-containing pesticides, fungicide, bactericide, oxidative stress.

1. INTRODUCTION

For centuries, pesticides have been used in agricultural practice to enhance food production by controlling unwanted pests [2]. Many of these pesticides used extensively worldwide are copper-based formulations, including copper sulfate, copper oxychloride and copper carbonate. Pesticides containing copper have a historical significance in that the fungicidal properties of "Bordeaux mixture", named after the Bordeaux region in France, were accidentally discovered. When Bordeaux mixture, a chemically undefined mixture of copper sulfate and hydrated lime, was applied to grapes to discourage local pilfering, it was observed that downy mildew disappeared from the treated plants. It was from this serendipitous event that commercialization of fungicides originated [19].

USEPA (2008) listed copper as a pesticide and copper compounds are extensively used in various agricultural settings. Millions tons of copper are applied annually, predominantly in crop protection [64]. Copper is relatively safe from a handling perspective, but there is some concern regarding its buildup in agricultural soils. After application on plants in the field, residual Cu typically accumulates in the upper 15 cm of soil, bound to the organic matter and fine clay fraction [29]. Most

importantly, the ecological risk assessments indicate that copper is relatively non toxic for use as a broad-spectrum fungicide on many food and ornamental crops, and for direct use in water applications as an algicide, aquatic herbicide, bactericide, and molluscicide. Copper compounds also are registered for antimicrobials [67].

Copper-based agrochemicals can affect human health, causing different types of cancer, degenerative diseases, and many immune, hematological, neurological and reproductive disorders [50].

With the increasing interest in improving "old" copper-containing pesticides and especially in developing new organic pesticides, it becomes of considerable practical importance to understand molecular mechanisms of copper action. This review article describes the metabolism, toxicity and several mechanisms of oxidative stress induction by copper and copper-containing pesticides in living organisms.

2. METABOLISM OF COPPER IN LIVING ORGANISM

Copper is absorbed, transported, distributed, stored, and excreted in the body according to complex homeostatic processes which ensure a constant and sufficient supply of the micronutrient while simultaneously avoiding excess levels [56]. It is mainly absorbed through the gastrointestinal tract of animals. From 20 to 60% of the dietary copper is absorbed, with the rest being excreted through the faeces. Various factors influence copper absorption. For example, copper absorption is enhanced by ingestion of animal protein, citrate, and phosphate. Copper ions are better adsorbed from salts, including copper gluconate, copper acetate, or copper sulfate, are more easily absorbed than from oxides [63]. Elevated levels of dietary zinc and cadmium, as well as high intakes of phytate and simple sugars (fructose, sucrose) inhibit dietary absorption of copper [12, 67, 68]. Following the metal passes through the basolateral membrane, it is transported to the liver bounded to the serum albumin. The transport of copper to the peripheral tissues is performed via the plasma attached to serum albumin, ceruloplasmin, or low-molecular-mass complexes [24]. In blood, copper is distributed into a non-exchangeable red cell pool, a plasma pool associated with proteins, and a labile pool of low molecular mass complexes. In humans, approximately 80-90% of the plasma copper is tightly bound with ceruloplasmin while the rest is bound to albumin and amino acids.

Bury et al. (2003) showed that in the fish gills, Cu^{2+} is probably reduced to Cu^+ and enters body via either a putative epithelial sodium channel (EnaC) or copper transporter 1 (CTR1). Metallochaperones (MC) bind Cu^+ and transport it to the Golgi network (GN), where copper enters into the Golgi lumen via a Menkes Cu^+ -ATPase (MNK). Cu^+ is incorporated into metal binding proteins (MBP) within the GN. The vesicles of GN then transfer copper to the basolateral membrane for release via exocytosis. Other ATPases exporting copper (i.e. Ag^+/Cu^+ -ATPase) may also be presented in the basolateral membranes. Intestinal export of copper may be realised via a Cu^-/Cl^- -symporter, or via the MNK pathway. Excess of copper is bound to low molecular mass proteins, such as metallothioneins (MT) (Fig. 1) [8].

Interestingly, in mammals intestinal copper uptake primarily occurs in the small intestine [67], whereas in fish, copper uptake is found on the mid/posterior region [23].

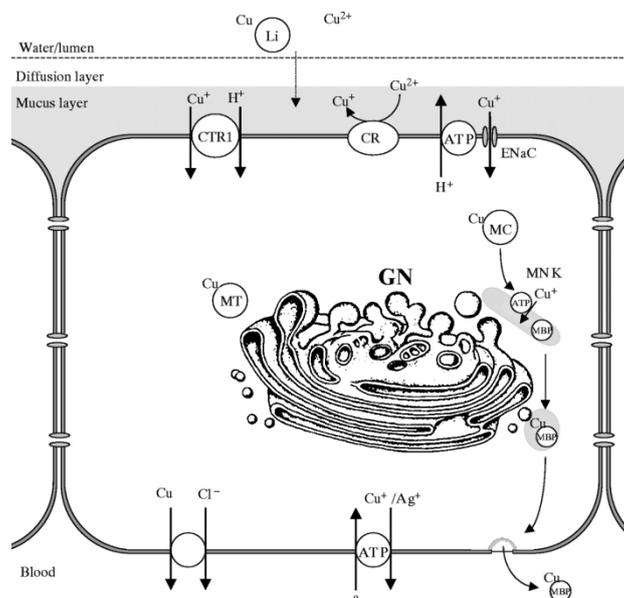


Fig. 1. Hypothetical representation of cellular copper uptake pathways in fish, combined data from gills and intestine (modified from [8]). *EnaC*, epithelial sodium channel; *CTR1*, copper transporter 1; *MC*, metallochaperones; *GN*, Golgi network, *MNK*, Menkes Cu^+ -ATPase; *MBP*, metal binding proteins; *Li*, aquatic ligand; *CR*, copper reductase.

Liver is the major organ involved in copper homeostasis [22, 31]. It accumulates a large proportion of the copper absorbed from the diet or water, and is the site for synthesis of the most abundant copper-containing protein in the body, ceruloplasmin. Ceruloplasmin is secreted into the blood and acts as a source of copper to extrahepatic organs [24]. Copper may also circulate in the body in complex with albumin and other low-molecular mass proteins [24]. The bile is the main site for secretion of excess copper in teleost fish [22]. In mammals, there are three possible secretory pathways: (1) a Cu -ATPase, identified in patients suffering from Wilson's disease (termed Wilson's protein or ATP7B) [24]; (2) a multiorganic cation transporter (cMoat) [16] and (3) lysosomal secretion [21]. Upon entering the cell through the copper transporter *CTR1*, copper is delivered to ATP7B in the Golgi apparatus by the copper chaperone ATOX1. In the Golgi apparatus copper is incorporated in various cuproenzymes including ceruloplasmin. When copper levels in the cell rise, ATP7B redistributes to a vesicular compartment. Upon relocalization of ATP7B, copper is excreted from the hepatocyte through the bile via an unknown mechanism that probably involves COMMD1 (Fig. 2) [13].

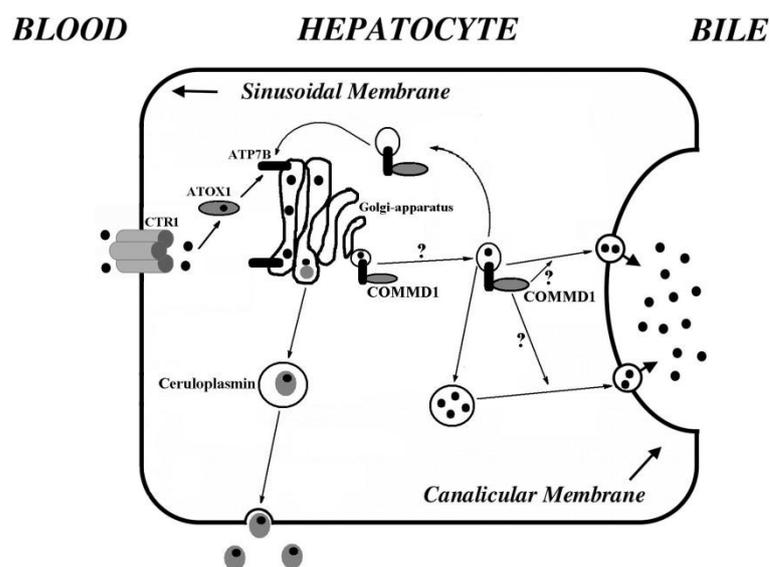


Fig. 2. The ATP7B-mediated copper export pathway in the hepatocytes (modified from [13]). *CTR1*, copper transporter 1; *ATOX1*, copper chaperone ATOX1; *ATP7B*, Wilson's protein; *COMMD1*, copper metabolism (Murr1) domain-containing protein 1.

In baker's yeast, copper is transported into the cell by two high-affinity copper transporters Ctr1 and Ctr3, or by a low-affinity Cu/Fe-transporter Fet4, depending on extracellular copper concentrations. Ctr2 could be involved in copper efflux from the vacuole. Copper is distributed via unknown mechanism to three different metallochaperones: Atx1, CCS and Cox17 [51]. Transport of copper to the secretory compartment involves the metallochaperone Atx1, that shuttles copper to Ccc2, a P-type ATPase located in the trans-Golgi network, and is responsible for Cu translocation. When Cu is transported into the lumen of the secretory pathway, it is loaded on Fet3, a multicopper-ferroxidase essential for high-affinity iron uptake that partners with the Ftr1 subunit. The delivery of copper to Sod1 is mediated by the copper chaperone for SOD, CCS. This protein contains three different domains: an Nt domain I similar to Atx1, a central domain II with homology to Sod1 and an essential Ct domain III. CCS directly interacts with Sod1 through the central domain and contacts from domain III to form a heterodimer. The metallochaperone Cox17 transports copper to Sco1, and other proteins, located in the inner mitochondrial membrane. Then copper is transferred to specific subunits of COX (Fig. 3) [51].

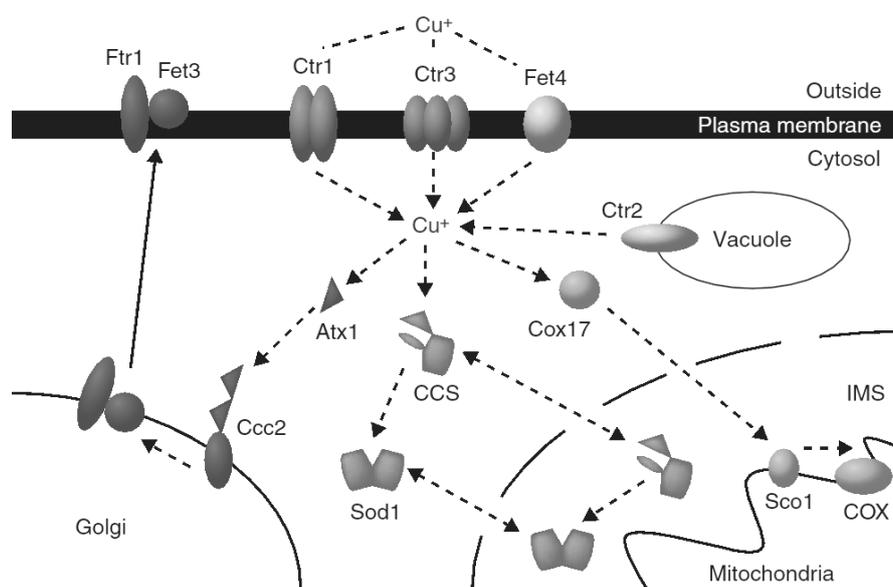


Fig. 3. Copper transport and distribution in baker's yeast (modified from [51]).
 Ctr1, Ctr2, Ctr3, Ctr4, copper transporters; Ftr1, Fet3, Fet4, Cu/Fe-transporters; Atx1, Cox17, CCS, metallochaperones; Ccc2, P-type ATPase; Sod1, Cu,Zn-SOD; Sco1, cytochrome C oxidase assembly protein; COX, cytochrome oxidase; IMS, intermembrane space.

3. COPPER AS A COMPONENT OF PESTICIDES

The first registration for a copper-containing pesticide, copper sulfate, was issued in 1956 [52]. Currently, 16 copper active ingredients have active food use registrations subject to tolerance reassessment and reregistration review [64].

Copper-based pesticides include aqueous solutions, wettable powders, dry flowables, dusts, flowables, water-dispersible granules, emulsifiable concentrates, and granules. There are two broad categories of copper-based products. Among them water soluble, such as copper sulphate, and insoluble in water, such the oxychlorides (Coppox®WG) and hydroxides (Hydrocop®WG). Water-soluble formulations are short lived, whereas the insoluble products release active copper ions over a period of time and are comparatively stable in nature. Concentrated water dispersible granules with additives, which ensure effective dispersion, also referred to as Dry Flowable Formulations seems are the most advanced user-friendly formulations [11].

Copper pesticides are formulated into various forms of copper, i.e., different salts and complexed forms, which ultimately dissociate into the cupric ion, the active component of concern. Among the copper-containing pesticides most common are the following: "Algimycin PWF" (copper in the form of

chelates of copper citrate and copper gluconate), a suspension concentrate formulation containing 5% metallic copper equivalent; "Macc 80" (Bordeaux mixture), a wettable powder formulation containing 200 g/kg of Cu; "Cuproxat SC" (tribasic copper sulfate), a suspension concentrate formulation containing 190 g/L of Cu; "Kocide 101" (copper hydroxide), a wettable powder formulation containing 500 g/kg of Cu; "Cuprocaffaro WP" (copper oxychloride), a wettable powder formulation containing 500 g/kg of Cu; "Nordox 75 WG" (copper (I) oxide), a wettable granule formulation containing 750 g/kg Cu; "MicroPro 200C-TS" (copper carbonate), a suspension concentrate formulation containing 28 % metallic copper equivalent; "Cutrine®-Plus" (copper ethanolamine complex), a suspension concentrate formulation containing 9 % metallic copper equivalent (Tab. 1) [11].

<i>Copper-based pesticide</i>	<i>Active ingredient</i>	<i>Use pattern(s)</i>
Copper (metallic)	Copper (metallic)	Algaecide, antifouling paint
Algimycin PWF	Copper (metallic in the form of chelates of copper citrate and copper gluconate)	Algaecide, fungicide, bactericide
Macc 80 (Bordeaux mixture), Cuproxat SC	Copper sulfates	Fungicide, algaecide, bactericide, herbicide, desiccant
Kocide 101, Copperhycide WP, Champion WP, Copperhycide WP, Hydrocop®WG, Zoom WP	Copper hydroxide	Bactericide, fungicide, plant growth regulator, wood preservative, antifouling paint
Cuprocaffaro WP, Rolex WP, Q-Copper WP, Curenox WP, Coppox®WG, Copral WP	Copper oxychloride	Algaecide, bactericide, fungicide
Nordox 75 WG, Caocobre, Fungi-Rap	Copper (I) oxide	Algaecide, wood preservative, antifouling paint
MicroPro 200C-TS	Copper carbonate	Algaecide, herbicide, wood preservative
Cutrine®-Plus	Copper ethanolamine complex	Algaecide, wood preservative

Tab. 1. Use patterns of copper-based pesticides.

4. TOXICITY OF COPPER AND COPPER-CONTAINING PESTICIDES TO TARGET ORGANISMS

Bacteria, fungi, and mollusks are generally the most sensitive to Cu compared with flowering plants and vertebrate animals. Common applications include controlling fungi in plants; controlling roots and other plant growth in sewers; controlling algae in swimming pools, ponds and lakes; controlling aquatic plant growth on boat hulls; serving as biocides in commercial products; and preventing rot and mildew on wood, roofing and other outdoor surfaces.

4.1. PLANTS AND ALGAE

The metal copper is a trace element essential as a micronutrient for cyanobacteria, algae and higher plants at low concentration because it is a reactant in biochemical functions of photosynthetic organisms, but at high concentrations it can be toxic [4]. In the later case, copper is very toxic for algae. It increases permeability of the cell membranes and leakage of the cellular constituents. However, the most important effect of copper on plants and algae is associated with the inhibition of photosynthesis. At high concentrations, it can be toxic by interrupting electron transport through photosystem II (PSII) [7]. The reaction center of PSII composes of a heterodimer of two integral membrane proteins, named D₁ and D₂ which bind electron transfer prosthetic groups such as P₆₈₀, pheophytin, and plastoquinon. PSII uses light energy to drive two chemical reactions – oxidation of water and reduction

of plastoquinone. The photosystem II complex is composed of more than fifteen polypeptides and at least nine different redox components (chlorophyll, pheophytin, plastoquinone, tyrosine, Mn, Fe, cytochrome b_{559} , carotenoids and histidine) [14, 42]. However, only five of these redox components are known to be involved in electron transport from H_2O to plastoquinone pool. There are also water oxidizing manganese cluster (Mn)₄, amino acid tyrosine, reaction center chlorophyll (P_{680}), pheophytin, and plastoquinone molecules, Q_A and Q_B .

Inhibition of oxygen evolution accompanied by quenching of variable fluorescence is the most apparent effect of the toxic action of copper on PSII [3, 26]. However, the precise location of the copper inhibitory binding site is still unknown. Most authors relate the target of the Cu-inhibition of PSII to its oxidizing side [7, 54, 55]. At higher copper concentrations, primary quinone acceptor Q_A [27], pheophytin- Q_A -Fe region [70], non-haem iron [28], and secondary quinone acceptor Q_B [44] were identified as the target sites of Cu inhibitory action on the acceptor side of PSII (Fig. 4). Schroder et al. (1995) showed that Cu specifically inhibited the electron donation from Tyr_z to P_{680} , either by a modification of this amino acid in D_1 protein and/or its microenvironment [57]. Furthermore, it was demonstrated that the central magnesium atom of chlorophyll can be substituted by several metals (e.g., mercury, copper or cadmium), damaging the photosystem [34].

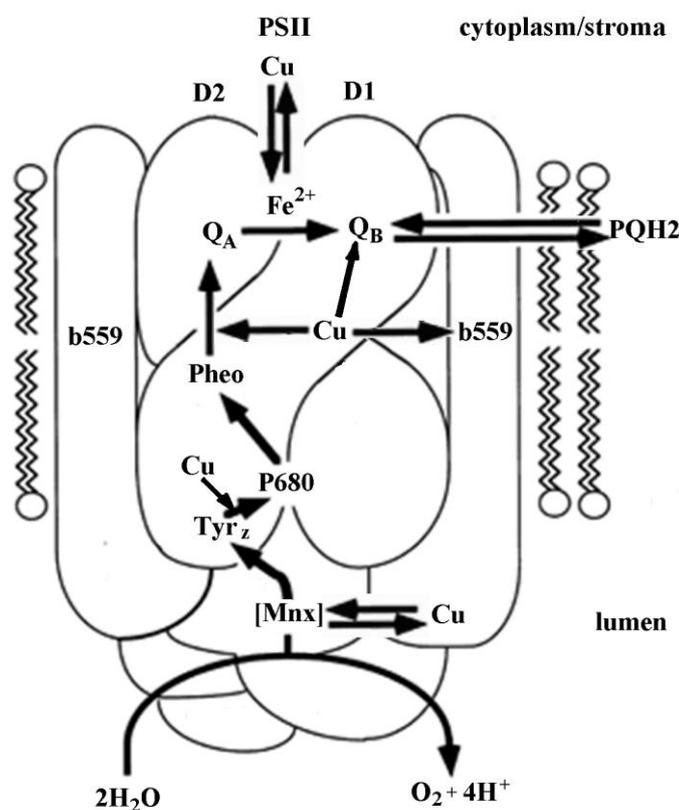


Fig. 4. Cu-inhibitory sites and action sites of different electron donors and acceptors in PSII-mediated electron transport. PSII, photosystem II; D_1 and D_2 , bind the electron carriers involved in transfer of electrons from Tyr_z to plastoquinone; b_{559} , cytochrome b_{559} ; Tyr_z , tyrosine; Pheo, pheophytin; Q_A and Q_B , bound plastoquinone; P_{680} , reaction center of chlorophyll (primary electron donor); PQ, reduced plastoquinone.

Cytochrome b_{559} is a heme protein and an essential component of all photosystem II reaction centers. If the membrane lacks cytochrome, a stable PS II reaction center cannot be formed [69]. It was also found that copper ions oxidized directly the low potential form cyt b_{559} at low concentrations (1-10 μM) and the high potential form at higher concentrations (10-100 μM), probably by deprotonation of this labile cyt b_{559} form [7].

Copper-induced inhibition of photosynthesis was found to be strongly related to the production of reactive oxygen species (ROS), since a number of studies reported activation of the antioxidant defense system, as well as an increase in the levels of ROS-modified lipids and proteins [15, 38]. Nevertheless,

all investigations on the specific Cu inhibitory binding site imply direct interference of the metal ion with the photosynthetic apparatus, resulting in a reduced electron flow.

4.2. FUNGI, BACTERIUM AND MOLLUSKS

Copper is a relatively non-specific bactericide and fungicide and can kill naturally occurring microorganisms on leaves as well as those that have been applied as biocontrol including *Bacillus sp.*, *Trichoderma* and others [52].

Copper fungicides may be grouped into three general types: basic salts, normal salts, organic complexes. By far the greater part of all research on copper fungicides has been focused on Bordeaux mixture, including attempts to explain the nature of fungicidal action. Most copper fungicides are applied as foliar sprays.

Following absorption into the fungus or bacterium, the copper ions will link to various chemical groups (imidazoles, phosphates, sulfhydryls, hydroxyls) presented in many proteins and disrupt the function of these proteins and enzymes, resulting cell damage and membrane leakage [43, 52]. Thus, the mode-of-action of copper hydroxide (or any other copper fungicide) is the nonspecific denaturation (disruption) of cellular proteins.

The toxic copper ions are absorbed by the germinating fungal spores and thus for best results copper must be reapplied as plants grow to maintain coverage and prevent disease establishment [39, 40]. Up to now, little is known about mechanisms of copper induced killing before it permeation into the spore.

Copper containing compounds are among most effective for bacterial diseases including *Erwinia* soft rot (calla, orchid and poinsettia), *Pseudomonas* leaf spots (bedding plants) and *Xanthomonas* leaf spots (geranium, ranunculus and zinnia). Copper products can also react with other mode-of-action group, in the conditions of bacterial diseases or resistance development to copper. Additionally, in mollusks, copper sulfate disrupts surface epithelia function and peroxidase enzymes [52].

5. TOXICITY OF COPPER AND COPPER-CONTAINING PESTICIDES: NON-TARGET ORGANISMS

5.1. AQUATIC ORGANISMS

Increased copper concentrations in the aquatic ecosystems can occur naturally but can also be related to different anthropogenic sources, e.g., agricultural fungicide and herbicide runoff [37]. Copper is highly toxic to most aquatic species. The main reason of copper toxicity to fish and aquatic invertebrates is rapid binding of copper to the gill membranes, causing damage and disturb osmoregulatory processes. The amount of cupric ion in the environment, and its toxicity to aquatic animals due to gill damage, depend on a number of water quality parameters including pH, alkalinity, and dissolved organic carbon [17].

Copper sulfate is toxic to aquatic invertebrates, such as crabs, shrimps, and oysters. It is used as a pesticide to control tadpole shrimp in rice production. The 96-hour LC₅₀ of copper sulfate to pond snails is 0.39 mg/L at 20 °C. Higher concentrations of the material caused some behavioral changes, such as secretion of mucous, and discharge of eggs and embryos [17].

5.2. TERRESTRIAL ORGANISMS AND HUMAN HEALTH

There is some uncertainty in the finding of risk to birds and mammals because, although copper is toxic at high concentrations, it is also an important essential trace element for terrestrial animals [17]. Many terrestrial animals have the ability to cope with some amount of excess copper exposure by storing it in the liver and bone marrow. Laboratory toxicity studies demonstrated that exposure to high levels of copper in the diet can overwhelm the ability of birds and mammals to maintain homeostasis. However, animals which are repeatedly exposed to levels of copper which do not cause permanent harm may undergo enzymatic adaptation which allows them to cope with greater levels of exposure [64].

Most agrochemicals, in particular copper-based formulations, seem to be responsible for several adverse effects on human health. These problems include different types of cancer, degenerative diseases, and many immune, hematological, neurological and reproductive disorders [50].

Toxic response in humans has been observed at concentration 11 mg/kg of copper. Ingestion of copper sulfate is often not toxic because vomiting is automatically triggered by its irritating effect on the gastrointestinal tract. However, the acute toxicity of copper-containing pesticides is not attributed to systemic toxicity, but to the efforts of the body to equilibrate copper concentrations [52]. Skin contact may result in itching or eczema. Copper is a skin sensitizer and can cause allergic reactions in some individuals. Eye contact with this material can cause conjunctivitis, inflammation of the eyelid lining, cornea tissue deterioration, and clouding of the cornea (Fig. 5) [17]. Ingestion of copper sulfate irritates the digestive system and may cause emesis and limiting toxicity. Copper hydroxide is less acutely toxic than copper sulfate, with an oral LD₅₀ in rats of 833 mg/kg. It is also not readily absorbed through the skin, with a dermal LD₅₀ of over 5000 mg/kg in rats [46]. Tissue corrosion, shock and death may occur after exposure to large doses of copper. Damage to blood cells, liver and kidney has also been reported [32].

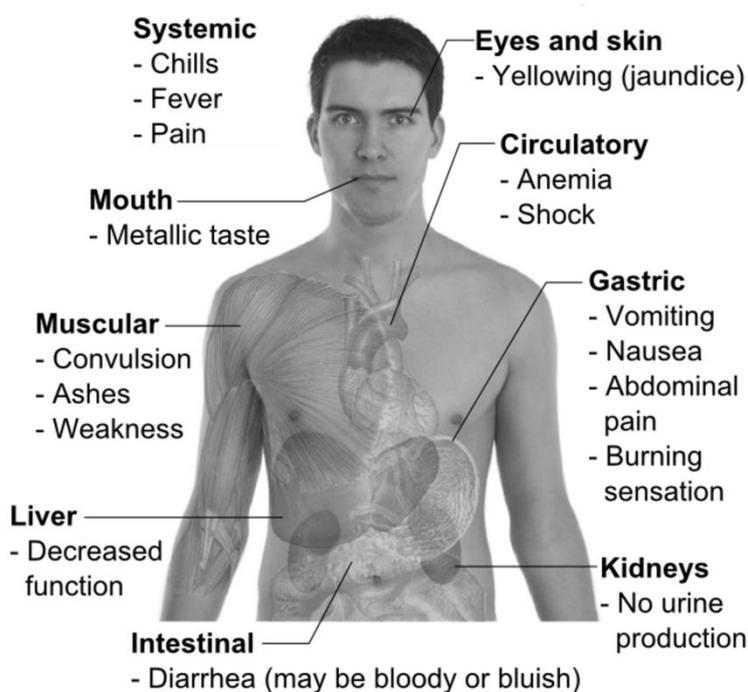


Fig. 5. Main symptoms of copper poisoning (by Mikael Häggström).

Irritant effects from occupational exposures to copper-based pesticides have been fairly frequent, including allergic reactions, itching, and eczema. Early signs and symptoms of copper poisoning include a metallic taste, nausea, vomiting, and abdominal pain. Chronic effects have been reported with vineyard workers who experienced liver disease after 3 to 15 years of exposure to Bordeaux mixture. The EPA does not require data on the teratogenic, mutagenic, carcinogenic, and reproductive effects on mammals for many of the copper-based pesticides [19].

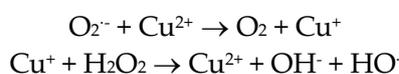
Copper imbalances in humans lead to serious diseases such as Menkes syndrome or Wilson disease, characterized by the inability to appropriately distribute copper to all cells and tissues [41]. Additionally, copper has been strongly implicated in neurodegenerative diseases such as familial amyotrophic lateral sclerosis, Alzheimer's disease, and prion diseases of neuronal spongiform encephalopathy [60].

6. COPPER AS ACTIVE INGREDIENT OF PESTICIDES AND OXIDATIVE STRESS

Copper as active ingredient of different pesticides found in all living organisms. It is absolutely necessary for survival and plays a crucial role as a catalytic cofactor in mammals in the active site of proteins, such as cytochrome c oxidase, tyrosinase, lysyloxidase, *p*-hydroxyphenyl pyruvate hydrolase, dopamine beta hydroxylase, and Cu,Zn-superoxidase dismutase (Cu,Zn-SOD). However, excessive amounts of Cu can oxidize important biomolecules, such as lipids, proteins, and DNA, mainly through the Fenton reaction [20]. Perturbations in copper concentrations in living organisms can cause oxidative stress.

Many researchers found adverse effects both *in vivo* and *in vitro* of Cu overload [5, 25, 33, 62]. Copper injection demonstrated the modification of activities of antioxidant enzymes. Enhanced concentrations of copper in living organisms caused increase in the activities of Cu,Zn-SOD and glutathione-S-transferase and decrease in the activities of catalase and selenium dependent glutathione peroxidase [35, 36].

Free Cu ions can be involved in ROS generation. Both cupric (Cu²⁺) and cuprous (Cu¹⁺) ions can participate in oxidation and reduction reactions to form hydroxyl radicals via the Haber-Weiss reaction [6]:



Generation of hydroxyl radicals has been confirmed by analysis of the products of DNA damage [20, 30]. Copper binds readily to DNA to form adducts. The endogenous DNA-associated copper could promote local production of hydroxyl radicals and hence oxidative damage to DNA. The fact that copper accumulates within the nucleus at copper overload obviously enhances the likelihood of such reactions occurring [53]. In this case, formed complex Cu-DNA promotes hydroxyl radical-dependent DNA fragmentation.

Stimulation of lipid peroxidation is one of the main consequences of copper-induced production of ROS. This has been manifested as increased production of pentane and hepatic malondialdehyde when liver homogenates or hepatocytes are exposed to ionic copper. Moreover, dietary copper overload in rats resulted in *in vivo* peroxidation of mitochondrial membrane lipids demonstrated by increased concentrations of conjugated dienes and thiobarbituric acid-reacting substances (TBARS) [25, 58]. Copper-catalyzed lipid peroxidation also appears to underlie the alterations in hepatocyte lysosomes in copper-loaded rats [45]. Concentrations of TBARS in the isolated lysosomal membranes of these rats doubled, with an increase in their fragility and decrease in their fluidity. There were also changes in the membrane content of selected fatty acids, with an increase in polyunsaturated fatty acids. Lysosomal pH also increased and these membrane alterations might affect the function of the proton ATPase pump [6].

Cu-overloaded rats exhibited oxidative injury including decreased levels of hepatic GSH and α -tocopherol, increased levels of mitochondrial lipid peroxidation products, decreases in state 3 respiration of mitochondria and the respiratory control ratio in hepatic mitochondria, and decreased complex IV (cytochrome c oxidase) activity [58].

Similar to Cu overload, Cu deficiency also increased cellular susceptibility to oxidative damage, which might account for some of the pathological changes observed with low Cu status [47]. Predictably, the activities of Cu,Zn-SOD and ceruloplasmin are sensitive to tissue Cu as these enzymes require Cu as a catalytic cofactor. A Cu deficiency-induced decrease in the activities of these enzymes in humans and animals was found [48, 65]. Erythrocytes from Cu deficient rats reduced Cu, Zn-SOD activity and increased oxidative damage to several subunits of erythrocyte spectrin [61]. A deficiency of Cu also decreases the activities of certain non-Cu containing enzymes of the antioxidant defense system including catalase and selenium-dependent glutathione peroxidase [10, 59]. Cu-deficient rats exhibited increased liver lipid peroxidation, elevated hepatic Fe level, hepatic and blood glutathione and blood cholesterol concentrations [9, 18]. Furthermore, oxidative DNA damage was also detected in Cu-

deficient tissues and cells. For example, cytogenetic analysis of lymphocytes from cattle showed a significant negative association between plasma Cu concentrations and frequency of chromosomal aberrations [1].

8. CONCLUSIONS

Copper is an essential nutrient and a redox-active transition metal that may initiate oxidative damage. Virtually all organisms require copper as a catalytic cofactor for biological processes such as respiration, iron transport, oxidative stress protection, peptide hormone production, pigmentation, blood clotting and normal cell growth and development. Copper-containing pesticides primarily used as fungicides to control bacterial and fungal diseases of fruits, vegetables, nuts and field crops. Some of the diseases that are controlled by these fungicides include mildew, leaf spots, blights and apple scab. They are also used as an algacide, an herbicide in irrigation and municipal water treatment systems, and as a molluscicide, a material used to repel and kill slugs and snails. Copper also participates in redox reactions that generate hydroxyl radical, which causes catastrophic damage to lipids, proteins and DNA. Additionally, Cu-induced oxidative damage has been implicated in disorders associated with abnormal Cu metabolism and neurodegenerative changes. Additionally, a deficiency in dietary Cu also increases cellular susceptibility to oxidative damage.

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Мета даної статті полягає в наданні короткого огляду сучасних знань про метаболізм та токсичність міді і мідь-вмісних пестицидів в живих організмах. Мідь є одним з важливих мікроелементів у всіх живих організмах (бактеріях, грибах, рослинах і тваринах), тому що вона бере участь у різних метаболічних процесах і підтримує важливі функції організмів. Транспорт і метаболізм міді в живих організмах в даний час є предметом багатьох досліджень. Мідь поглинається, транспортується, поширюється, зберігається, і виводиться з організму через комплекс гомеостатичних процесів, які забезпечують підтримання постійного рівня цього мікроелементу в організмі і уникнення його надмірних кількостей. Багато аспектів гомеостазу міді вивчалися на молекулярному рівні. Пестициди, активним інгредієнтом яких є іони міді, зокрема, фунгіциди, бактерициди і гербіциди, широко використовуються в сільськогосподарській практиці в усьому світі, що збільшує ризик інтоксикації даним металом. Надлишок міді в організмі має шкідливий вплив, оскільки він стимулює виробництво вільних радикалів у клітині, індукує пероксидне окислення ліпідів і порушує загальну антиоксидантну здатність організму. В цьому огляді мова йтиме про механізми токсичності міді та мідь-вмісних пестицидів.

Ключові слова: мідь, мідь-вмісні пестициди, фунгіциди, бактерициди, оксидативний стрес.