資料２－３

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(WHOガイドライン)

Copper

Copper levels in drinking-water are usually low at only a few micrograms per litre, but copper plumbing may result in greatly increased concentrations. Concentrations can reach several milligrams per litre following a period of stagnation in pipes.

Copper is an essential element, and the intake from food is normally 1-3 mg/day. In adults, the absorption and retention rates of copper depend on the daily intake; as a consequence, copper overload is unlikely. Acute gastric irritation may be observed in some individuals at concentrations in drinking-water above 3 mg/litre. In adults with hepatolenticular degeneration, the copper regulatory mechanism is defective, and long-term ingestion can give rise to liver cirrhosis.

Copper metabolism in infants, unlike that in adults, is not well developed, and the liver of the newborn infant contains over 90% of the body burden, with much higher levels than in adults. Since 1984, there has been some concern regarding the possible involvement of copper from drinking-water in early childhood liver cirrhosis in bottle-fed infants, although this has not been confirmed.

In 1982, JECFA proposed a provisional maximum tolerable daily intake (PMTDI) of 0.5 mg/kg of body weight, based on a rather old study in dogs. With an allocation of 10% of the PMTDI to drinking-water, a provisional health-based guideline value of 2 mg/litre (rounded figure) is calculated. This study did not take into account the differences in copper metabolism in the neonate. However, a concentration of 2 mg/litre should also contain a sufficient margin of safety for bottle-fed infants, because their copper intake from other sources is usually low.

In view of the remaining uncertainties regarding copper toxicity in humans, the guideline value is considered provisional. Copper can give rise to taste problems.

13.13 Copper

13.13.1 General description

Identity

Widely used copper compounds include $CuCl_2 \cdot 2H_2O$ (CAS no. 7447-39-4), $Cu(NO_3)_2 \cdot 3H_2O$ (CAS no. 10031-43-3), and $CuSO_4 \cdot 5H_2O$ (CAS no. 7758-99-8).

Physicochemical properties (1, 2)

Compound	*Water solubility (g/litre)*
$CuCl_2 \cdot 2H_2O$	710 at 0 °C; 1080 at 100 °C
$Cu(NO_3)_2 \cdot 3H_2O$	1380 at 0 °C; 12 700 at 100 °C
$CuSO_4 \cdot 5H_2O$	320 at 0 °C; 2030 at 100 °C

Organoleptic properties

Dissolved copper imparts a colour and an unpleasant astringent taste to drinking-water *(3)*. Staining of laundry and plumbing fixtures occurs when copper concentrations in water exceed 1 mg/litre. The taste threshold is above 5 mg/litre, although taste is detectable in distilled water at 2.6 mg/litre *(4)*. The organoleptic threshold of dissolved Cu^{2+} is 0.8 - 1.0 mg/litre in mineral water and 2.4 - 3.2 mg/litre in 5 mmol/litre saccharose *(5)*.

Major uses

Copper is an important heat and electrical conductor. It is also used for water pipes, roof coverings, household goods, and chemical equipment, in the arts, and in many alloys (e.g. brass and bronze). Copper oxides, chlorides, sulfates, ethanoates, bromides, and carbonates are widely used in pest control, as inorganic dyes, as feed additives, in photography, in seed disinfectants, as fungicides and algicides, and in electroforming *(1, 2, 6)*.

Environmental fate

Monovalent copper is unstable in aqueous solution. Only those copper(I) compounds that are insoluble in water (Cu_2O, Cu_2S) and certain copper(I) complexes are stable in aqueous environments. Cu(II) forms complexes with both inorganic and organic ligands such as ammonium and chloride ions and humic acids *(2)*.

13.13.2 Analytical methods

The most important methods for the determination of copper and their detection limits are atomic absorption spectrometry with flame detection (1.5 µg/litre) or in the graphite furnace (60 ng/litre); pulse inverse voltammetry (1 ng/litre); spectral photometry (100 µg/litre); neutron activation (0.2 ng of copper per 500 mg solid sample); and emission spectroscopy (0.5 µg/litre) *(6, 7)*.

13.13.3 Environmental levels and human exposure

Air

Copper concentrations in air in rural areas in the USA and Europe are normally below 10 ng/m^3. In urban areas, concentrations may be as high as 1500 ng/m^3 *(6, 8)*, although levels around 25 ng/m^3 have also been found *(6)*.

Water

Natural copper concentrations in drinking-water are around a few micrograms per litre *(6)*. Depending on such properties as hardness, pH, anion concentrations, oxygen concentration, temperature, and the technical conditions of the pipe system *(1, 6)*, water from copper pipes may contain several milligrams of copper per litre *(1, 9)*. In a sample of water for human consumption which had remained stagnant for 12h, an extreme level of 22 mg of copper per litre was found *(10)*.

Food

Foods especially rich in copper (10 - 100 mg/kg) are veal and pig, sheep, and calf liver. Chocolate and chocolate products, tea, and coffee (dry) can also contain more than 10 mg of copper per kg. Other foods may contain up to 10 mg/kg (nuts), median values being around 2 mg/kg *(1, 11)*.

Estimated total exposure and relative contribution of drinking-water

Copper is ingested by humans mainly via food and drinking-water. In two 24-h intake studies in the Netherlands, the average daily copper intake per person was 1.2-1.4 mg *(1)*. Intakes of 1.82-2.38 mg/day *(11)* and less than 0.95 mg/day (duplicate study) *(12)* have been reported in the western and eastern parts of Germany, respectively; intakes in the USA were 2-4 mg/day *(6)*. Drinking-water can contribute a significant proportion of the daily copper intake if it has flowed through copper installations *(1, 6)*.

13.13.4 Kinetics and metabolism in laboratory animals and humans

Up to 100% copper absorption was observed in newborn rats. After weaning, absorption rates fell in various animal species to below 10% *(13)*. Estimated values for intestinal copper absorption in humans vary between 25% and 65% *(13)*. In adults, the absorption and retention rates of copper depend on the daily intake and, as a consequence, copper overload is unlikely. In a balance study with bottle-fed infants, absorption and retention rates were 23.9% and 21.9% of intake, respectively *(14)*.

Copper is an essential element. Balance studies on adults suggest that a copper intake of 1 - 5 mg/day, corresponding to 20 - 80 µg/kg of body weight per day *(15, 16)* is required. The normal copper content in the adult is 1 - 2 mg/kg of body weight. In neonates, the liver contains over 90% of the total body copper (4-5 mg/kg of body weight); the copper concentration in the newborn liver is 6-10-fold higher than in the adult liver *(17)* but decreases during the first 3 months of life *(18)*.

Normal copper concentrations in plasma are 0.9-1.3 mg/litre *(17)*. Of this, 5-10% is bound to albumin and 90-95% specifically to the copper transport protein ceruloplasmin *(8, 13)*. In the liver, copper is bound mainly to metallothionein but also to functionally specific enzymes *(19)*; glutathione serves as a buffer to trap free copper ions that would otherwise be toxic *(20)*. Partial saturation of metallothionein with copper and zinc in the liver of the newborn depends on the cytosolic zinc: copper ratio *(18)*.

About 1 mg of copper per day is transported to the tissues bound to ceruloplasmin *(15, 16)*. Excretion takes place primarily via the faeces; urine contains only 0.5-3% of the daily intake *(6, 21, 22)*.

13.13.5 Effects on laboratory animals and *in vitro test* systems

Acute exposure

Depending on the animal species and the anion of the copper salt administered, oral LD_{50}s vary between 15 (guinea-pig: $CuCl_2$) and 416 (rats: Cu(OH)Cl; Cu_2O) mg/kg of body weight *(13, 21, 22)*.

Short-term exposure

In most studies with rodents, copper given orally in doses of up to 50 mg/kg of body weight for less than 1 year caused either no effects or adaptation to copper exposure with transient signs of toxicity. No such adaptation was observed in rabbits, pigs, and sheep *(13, 21, 22)*, the last-named being especially sensitive to some of the acute effects of excess copper intake.

Long-term exposure

In two oral studies, NOAELs of 5 mg/kg of body weight per day (1 year; dog) and 160 mg/kg of body weight per day (2 years; rat) were found for the end-points liver functional changes (dog) and various macroscopic and microscopic pathological parameters (rat). In a 16-month rabbit study, a LOAEL of 12 mg/kg of body weight per day was estimated for cirrhosis-like hepatic changes *(21, 22)*.

Reproductive toxicity, embryotoxicity, and teratogenicity

Copper gluconate given orally to mice and rats at 30 mg/kg of body weight per day on days 6-14 and 5-15 of gestation, respectively, was neither embryotoxic nor teratogenic. In another assay with comparable exposure, the fertility of rats was not affected. A much higher NOAEL was reported with copper sulfate for skeletal deformations of fetuses from exposed mothers, but reduced maternal food intake could not be ruled out as the cause *(6, 21, 22)*.

Mutagenicity and related end-points

The results of mutagenicity tests are inconclusive *(6)*. Positive results from *in vitro* tests using free copper ions are not applicable to the *in vivo* situation, where copper is always tightly bound to low- and high-molecular-weight ligands *(18, 19)*.

Carcinogenicity

Based on the results of a number of animal studies involving oral and intraperitoneal exposure to various copper compounds, it is generally agreed that copper and its salts are not animal carcinogens *(6, 21, 22)*.

13.13.6 Effects on humans

Acute exposure

The lethal oral dose for adults lies between 50 and 500 mg of copper(II) salt per kg of body weight. Vomiting, diarrhoea, nausea, and some acute symptoms presumably due to local irritation by ingested copper(II) ions have been described in several case reports *(6, 21, 22)*. The estimated concentration of copper(II) in drinking-water or beverages that can lead to symptoms of this type is 30 mg/litre but may vary with the binding and chemical form of copper present.

Short-term exposure

Copper pipes in haemodialysis devices have caused systemic copper poisoning in patients *(21, 22)*. Drinking-water from a new copper kettle used over a period of 3 months for the preparation of food and beverages may have been responsible for a strongly enhanced serum copper level, behavioural changes, diarrhoea, and progressive loss of strength in a 15-month-old child *(23)*.

A 14-month-old infant died of micronodular liver cirrhosis, probably due to pre- and postnatal exposure to

up to 6.8 mg of copper per litre in the very acid water that had flowed through a copper installation and had been used to prepare the infant's feed *(24)*. A total of 22 similar cases of early childhood liver cirrhosis have been described in two limited areas in Germany *(25)*. The estimated daily copper intake that might have triggered the cirrhosis in the infants' early months of life *(26)* is at least 900 µg/kg of body weight, about 10 times their daily requirement *(21, 22)*.

Long-term exposure

In hepatolenticular degeneration (Wilson disease) which is caused by reduced copper excretion in the bile, the normal daily copper intake of a few milligrams is enough to trigger liver cirrhosis and excessive copper accumulation in many organs, but only after several years of exposure *(6, 27)*. The copper status of the healthy liver of neonates during the first few months of life is comparable to that of a person suffering from Wilson disease *(28)*, which may explain why infants are more sensitive to factors that threaten copper homoeostasis than are older children and adults *(25)*.

In a recent Finnish report, it was claimed that a positive correlation existed between coronary heart disease incidence and the plasma copper level under conditions of selenium malnutrition *(29)*. The duration and source of the excessive copper exposure in this study were not specified.

13.13.7 Provisional guideline value

Based on a NOAEL of 5 mg/kg of body weight per day for the end-point liver toxicity in a rather old 1-year study in dogs and in the light of the essentiality of copper, a provisional maximum tolerable daily intake (PMTDI) of 0.5 mg/kg of body weight was established by JECFA in 1982 *(21, 22)*. An allocation of 10% of the PMTDI to drinking-water gives a guideline value of 2 mg of copper per litre (rounded figure). Although this study did not take into account the differences in copper metabolism in the neonate, a concentration of 2 mg/litre should provide a sufficient margin of safety for bottle-fed infants because their copper intake from other sources is usually low. In view of the remaining uncertainties regarding copper toxicity in humans, however, this guideline value is considered provisional. Copper can give rise to taste problems, but the taste should be acceptable at the health-based provisional guideline value.

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