Effects on the liver. Cirrhosis and acute liver failure have been attributed to chronic excessive copper supplement ingestion.[1] Supplementation with 10 mg daily of copper (around the safe upper limit) for 2 months has been reported to be associated with transient mild increases in serum aminotransferase values.[2]

1. O'Donohue J, *et al*. Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. *Eur J Gastroenterol Hepatol* 1993; **5:** 561–2.
2. Araya M, *et al*. Supplementing copper at the upper level of the adult dietary recommended intake induces detectable but transient changes in healthy adults. *J Nutr* 2005; **135:** 2367–71.

Interactions

Large doses of zinc supplements may inhibit the gastrointestinal absorption of copper.

Uses and Administration

Copper is an essential trace element although severe copper deficiency, which is associated with anaemia, neutropenia, and bone demineralisation, is rare in humans. Copper sulfate is added to parenteral feeds as a source of copper in the prophylaxis and treatment of deficiency states. Doses that have been used for prophylaxis range from 0.5 to 1.5 mg (7.9 to 23.6 micromoles) of copper daily although up to 3 mg daily has been suggested in established deficiency; infants have received 20 micrograms/kg (0.3 micromol/kg) of copper daily. The dose should be governed by the serum-copper concentration, which in healthy adults ranges between 0.7 and 1.6 micrograms/mL (0.01 to 0.025 micromol/mL).

Copper sulfate and other soluble salts of copper have an astringent action on mucous surfaces and in strong solutions they are corrosive. Copper nitrate has been used in preparations for the removal of warts. The uses of copper acetate are discussed on p.2287.

Copper has a contraceptive effect (p.2070) when present in the uterus, and is added to some intra-uterine contraceptive devices; such devices are considered to be effective and safe for several years after insertion, and may be the most effective method for emergency contraception (p.2071). Copper is also reported to have an antimicrobial action.

Copper sulfate has been used to prevent the growth of algae in reservoirs, ponds, and swimming pools and as a molluscicide in the control of fresh-water snails that act as intermediate hosts in the life-cycle of the parasites causing schistosomiasis.

Reagents containing copper sulfate are used in tests for reducing sugars.

In veterinary medicine calcium copperedetate, copper methionate, copper oxide, and cuproxoline are used for the prevention and treatment of copper deficiency.

Copper bracelets are worn as a folk remedy for rheumatic disorders: there is no good evidence to justify such a practice.

Homoeopathy. Copper has been used in homoeopathic medicines under the following names: Cuprum metallicum; Cuprum; Cuprum met.; Cup. met.

Copper sulfate has been used in homoeopathic medicines under the following names: Cuprum sulfuricum; Cuprum sulphuricum; Cup. s.

◊ General references.

1. Wang T, Guo Z. Copper in medicine: homeostasis, chelation therapy and antitumor drug design. *Curr Med Chem* 2006; **13:** 525–37.

Deficiency states. Acquired copper deficiency is very rare and the small number of cases have usually involved patients on total parenteral nutrition or long-term enteral nutrition.[1] Copper deficiency may also be due to malnutrition,[2] malabsorption, or secondary to excessive zinc consumption.[3,4] Clinical manifestations of deficiency include hypocupraemia, hypoceruloplasminaemia, neutropenia, anaemia, osteoporosis, and fracture of the long bones.[2] However, cases may present with neurological signs resembling the subacute combined degeneration normally associated with vitamin B_{12} deficiency.[3,4] Effects on blood may be absent, and zinc concentrations normal;[3] however, hyperzincaemia may be seen even in the absence of exogenous zinc consumption.[4]

Menkes' disease is an X-linked genetic disorder associated with a defect in copper transport, which almost invariably results in death due to progressive cerebral degeneration by the age of 3 years.[5,6] Clinical features include skeletal abnormalities, severe mental retardation, thrombosis, hypothermia, arterial abnormalities, and characteristic facial features.[7] Early parenteral treatment with copper-histidine complex may be of benefit in such children.[5-8] Optimal response to copper therapy appears to occur only in patients who are identified in the newborn period and who have some residual copper-transport activity. More than 3 years of copper replacement therapy may not be necessary or desirable.[6]

1. Masugi J, *et al*. Copper deficiency anemia and prolonged enteral feeding. *Ann Intern Med* 1994; **121:** 386.
2. Cordano A. Clinical manifestations of nutritional copper deficiency in infants and children. *Am J Clin Nutr* 1998; **67** (suppl): 1012S–1016S.
3. Kumar N, *et al*. Copper deficiency myelopathy produces a picture like subacute combined degeneration. *Neurology* 2004; **63:** 33–9.
4. Kumar N. Copper deficiency myelopathy (human swayback). *Mayo Clin Proc* 2006; **81:** 1371–84.
5. Sarkar B, *et al*. Copper-histidine therapy for Menkes' disease. *J Pediatr* 1993; **123:** 828–30.
6. Kaler SG, *et al*. Neonatal diagnosis and treatment of Menkes disease. *N Engl J Med* 2008; **358:** 605–14.
7. Kirodian BG, *et al*. Treatment of Menkes disease with parenteral copper histidine. *Indian Pediatr* 2002; **39:** 183–5.
8. Cox DW. Disorders of copper transport. *Br Med Bull* 1999; **55:** 544–55.

Human requirements. In the UK dietary reference values (see p.1925) have been published for copper.[1] Although an estimated average requirement (EAR) could not be derived a reference nutrient intake (RNI) of 1.2 mg (19 micromoles) daily was set for adults; RNIs of lower values were also specified for infants and children.[1] The Expert Group on Vitamins and Minerals[2] have established a safe upper level (SUL) for copper of 160 micrograms/kg daily.

In the USA the recommended dietary allowance (RDA) for copper is 900 micrograms daily in adults, and the tolerable upper intake level is 10 mg daily.[3]

WHO has estimated a minimum population mean intake of 1.2 mg daily for women and 1.3 mg daily for men, and safe upper limits of population mean intakes of 10 mg daily for women and 12 mg daily for men;[4] values are also estimated for infants and children.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 10/11/05)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
4. WHO. Copper. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 123–43.

Schistosomiasis. Although most control programmes for schistosomiasis (p.138) use niclosamide as a molluscicide, and copper salts have largely been abandoned for snail control, WHO noted in 1993 that copper sulfate was still used for this purpose in Egypt.[1]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 21/07/08)

Preparations

BPC 1973: Compound Ferrous Sulphate Tablets;
USP 31: Cupric Chloride Injection; Cupric Sulfate Injection.

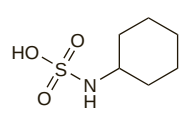
Proprietary Preparations (details are given in Part 3)
Austral.: Multiload; ***Braz.:*** Multiload; ***Canad.:*** Gyne-T†; ***Chile:*** Diuprotect; Multiload; Safety T; ***Denm.:*** Multiload; ***Fr.:*** Gynelle 375; Ionarthrol†; Metacuprol; Multiload; TT 380; UT 380; ***Ger.:*** femena; Multiload; ***Hong Kong:*** Flexi-T; Multiload; ***Indon.:*** Copper-T; ***Israel:*** Anticon; Mona-Lisa; Multiload; ***Ital.:*** Gravigard; Gynefix; Multiload; No-Gravid; Telo Cypro†; UT 380; ***Malaysia:*** Multiload; ***Mex.:*** Cuprifusin†; Multiload†; ***Neth.:*** Multiload†; ***NZ:*** Multiload; ***Port.:*** Multiload†; ***S.Afr.:*** Cuprocept CCL†; Dalcept†; Multiload†; Tricept†; ***Singapore:*** Multiload; Sof-T†; ***Switz.:*** Multiload; ***Thai.:*** Multiload; ***Turk.:*** Multiload; ***UK:*** Flexi-T; Gynefix; Multiload; ***USA:*** Paragard T380A; ***Venez.:*** Multiload.

Multi-ingredient: ***Arg.:*** Dermalibour; Nova-T; ***Austral.:*** APR Cream†; Ascoxal; ***Braz.:*** Belagin; Micotox†; Sulfato Ferroso Composto; Sulfatofer†; ***Canad.:*** Nova-T; ***Chile:*** Agua Sulfatada Picrica; Cicalfate; Nova-T†; Sebium H2O; ***Fin.:*** Ascoxal†; ***Fr.:*** Atoderm moussant; Cicalfate; Cicaplast; Cu-Zn; Decramp; Dermalibour; Dermo-Sulfuryl; Dermocuivre; Eryase; Nova-T; Oligoderm; Oligorhine; Oligorhine Manganese; Purif-Ac Emulsion; Purif-Ac Gel; Ramet Dalibour; Ramet Pain; Ruboderm Plus; Septalibour†; ***Ger.:*** Nova-T; Solco-Derman; ***Hong Kong:*** Aderma Dermalibour†; Cool Mint Listerine; Nova-T; Solcoderm; ***India:*** Hepatoglobine; ***Indon.:*** Nova-T; ***Irl.:*** Ferrotab†; ***Israel:*** Nova-T; ***Ital.:*** Cuprosodio; Cuprosodio Plus; Emmenoiasi; Inflamase; Nova-T; Rinogutt Atlantic; Sterimar Cu; ***Malaysia:*** Nova-T; Solcoderm†; ***Mex.:*** Ascoxal; Dalidome; Daribur; Nova-T; ***Neth.:*** Nova-T†; ***Norw.:*** Ascoxal†; ***NZ:*** Nova-T; ***Rus.:*** Solcoderm (Солкодерм); ***S.Afr.:*** Ferrous Sulphate Compound; Lotio Pruni Comp cum Cupro; Muscle Rub; Nova-T; ***Singapore:*** Nova-T; ***Swed.:*** Ascoxal†; ***Switz.:*** Nova-T; Solcoderm; ***Thai.:*** Nova-T†; ***Turk.:*** Nova-T; ***UK:*** Foresight Iron Formula; Nova-T; ***USA:*** ORA5; ***Venez.:*** Cianofer; Cobalfer; Fercobre†; Folifer B-12; Hepafol con B-12; Nova-T.

Cyclamic Acid *(BAN, USAN)*

Ciclámico, ácido; Cyclam. Acid; E952; Hexamic Acid. *N*-Cyclohexylsulphamic acid.

$C_6H_{13}NO_3S$ = 179.2.
CAS — 100-88-9.



Calcium Cyclamate

Calc. Cyclam.; Calcium Cyclohexanesulfamate; Ciclamato de calcio; Cyclamate Calcium; E952. Calcium *N*-cyclohexylsulphamate dihydrate.

$C_{12}H_{24}CaN_2O_6S_2.2H_2O$ = 432.6.
CAS — 139-06-0 (anhydrous calcium cyclamate); 5897-16-5 (calcium cyclamate dihydrate).

Potassium Cyclamate

Cyclamate potassium; HSDB 1239; Monopotassium cyclohexanesulfamate; potassium cyclohexanesulfamate. Potassium *N*-cyclohexysulphamate.

$C_6H_{12}NO_3SK$ = 217.3.
CAS — 7758-04-5.

Sodium Cyclamate *(BAN, rINN)*

Ciclamato de sodio; Cyclamate de Sodium; Cyclamate Sodium; E952; Natrii cyclamas; Natrio ciklamatas; Nátrium-ciklamát; Natriumcyklamat; Natrium-cyklamát; Natriumsyklamaatti; Siklamat Sodyum; Sod. Cyclam.; Sodium, cyclamate de; Sodium Cyclohexanesulphamate. Sodium *N*-cyclohexylsulphamate.

Натрия Цикламат

$C_6H_{12}NNaO_3S$ = 201.2.
CAS — 139-05-9.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Sodium Cyclamate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 10% solution in water has a pH of 5.5 to 7.5.

Profile

Cyclamic acid and its salts are intense sweetening agents. In dilute solutions (up to about 0.17%) sodium cyclamate is about 30 times as sweet as sucrose but this factor decreases at higher concentrations. When the concentration approaches 0.5%, a bitter taste becomes noticeable. It is stable to heat.

The use of cyclamates as artificial sweeteners in food, soft drinks, and artificial sweetening tablets was at one time prohibited in Great Britain and some other countries because of concern about the metabolite cyclohexylamine. However, after reappraisal their use is now allowed.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Kaldil Diet; ***Braz.:*** Sucaryl; ***Canad.:*** Sucaryl†; ***Turk.:*** Tadalin.

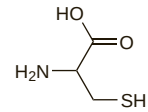
Multi-ingredient: ***Arg.:*** Rondo; Sucaryl; ***Austral.:*** Sucaryl; ***Braz.:*** Finn Cristal; ***Chile:*** Sucaryl†; Sukar-Sin; ***Fr.:*** Sucaryl; ***Israel:*** Sucrin; ***Ital.:*** Diet Sucaryl; ***NZ:*** Sucaryl; ***Port.:*** Dulceril†; ***Rus.:*** Zuckli (Цюкли); ***Turk.:*** Dolce; Dulcaryl.

Cysteine *(rINN)*

C; Cisteína; Cys; Cystéine; L-Cysteine; Cysteinum; E920; L-Cysteina. L-2-Amino-3-mercaptopropionic acid.

Цистеин

$C_3H_7NO_2S$ = 121.2.
CAS — 52-90-4.



Pharmacopoeias. In *Ger.*

Cysteine Hydrochloride *(rINNM)*

Cisteino hidrochloridas monohidratas; Cisztein-hidroklorid-monohidrát; Cys Hydrochloride; Cystéine, Chlorhydrate de; Cystéine (chlorhydrate de) monohydraté; L-Cysteine Hydrochloride Monohydrate; Cystein-hydrochlorid monohydrát; Cysteinhydrokloridmonohydrat; Cysteini Hydrochloridum; Cysteini hydrochloridum monohydricum; Hidrocloruro de cisteína; Kysteiinihydrokloridimonohydraatti; L-Cysteiny chlorowodorek. L-2-Amino-3-mercaptopropionic acid hydrochloride monohydrate.

Цистеина Гидрохлорид

$C_3H_7NO_2S,HCl,H_2O$ = 175.6.
CAS — 52-89-1 (anhydrous L-cysteine hydrochloride); 7048-04-6 (L-cysteine hydrochloride monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.
Ph. Eur. 6.2 (Cysteine Hydrochloride Monohydrate; Cysteine Hydrochloride BP 2008). A white or almost white crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. Protect from light.
USP 31 (Cysteine Hydrochloride). White crystals or crystalline powder. Soluble in water, in alcohol, and in acetone.

Profile

Cysteine is a non-essential amino acid. Cysteine and cysteine hydrochloride are used as dietary supplements.