

intake was believed to be above 25 micrograms daily for adults.¹ Similarly, in the USA a recommended dietary allowance has not been published but the adequate intake was estimated to be 35 micrograms daily for young men and 25 micrograms daily for young women.² WHO considers that the minimum population mean intake likely to meet normal needs for chromium might be about 33 micrograms daily, and that supplementation of this element should not exceed 250 micrograms daily until more is known.³

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. 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)
3. WHO. Chromium. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 155–60.

Supplementation. Although a daily chromium intake of 200 nanograms/kg has been suggested in children given total parenteral nutrition (TPN), a study in 15 children¹ given long-term parenteral nutrition found that supplementation at about this level was associated with serum-chromium concentrations 4 to 42 times higher than the mean value in 15 children not receiving TPN. Raised serum-chromium concentrations were associated with a decrease in glomerular filtration rate; one year after stopping chromium supplementation, which reduced intake to 50 nanograms/kg daily (as contaminants of water and TPN solutions), chromium concentrations, although lower, were still higher than controls and renal function had not altered. The authors subsequently ceased chromium supplementation in both children and adults, since chromium contamination of TPN solutions appeared adequate to prevent deficiency, although it was acknowledged that signs of chromium deficiency might take some years to appear. Chromium contamination in various preparations used in paediatric parenteral nutrition has been studied.²

1. Moukartzel AA, et al. Excessive chromium intake in children receiving total parenteral nutrition. *Lancet* 1992; **339**: 385–8.
2. Hak EB, et al. Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; **55**: 150–4.

Preparations

USP 31: Chromic Chloride Injection; Chromium Picolinate Tablets.

Proprietary Preparations (details are given in Part 3)

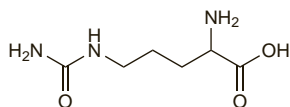
Arg.: NH4 Silhouette; Ripped Max; Sigmar Lipo; Tonekin; **Austral.:** Chrome; **Chile:** Edul K-200; **Fr.:** Chromasvelt; **Ital.:** Croben; **Mex.:** Cromifusin†; Ifa Slim†; **USA:** Chroma-Pak.

Multi-ingredient: **Arg.:** Centellacrom; Cholesterol Reducing Plan†; Garcia Cima Cambogia, Compuesta; Herbacccion Diet; IP-6; Metabolic; Novosulf†; Tonnekin Plus†; Top Life Diet†; **Austral.:** Bioglan 3B Beer Belly Buster; Citri Slim+Trim; Digestaid; Pro-Shape†; **Indon.:** Biochocles; Kitoles; Vitasilim; **Mex.:** Lipo Slim N†; Slim-D; **Philipp.:** Liposorb; Nutraft.

Citrulline

N^2 -(Aminocarbonyl)-L-ornithine; N^8 -Carbamylornithine; Citrullin; L-citrulline; NSC-27425. α -Amino- δ -ureidoveralaline.

$C_6H_{13}N_3O_3 = 175.2$
CAS — 372-75-8.



Profile

Citrulline is a non-essential amino acid that is involved in the urea cycle. Citrulline and citrulline malate are used as dietary supplements.

Hyperammonaemia. Citrulline has been given as an alternative to arginine in the management of hyperammonaemia (p.1929) due to urea cycle disorders.

Lysinuric protein intolerance is another condition associated with hyperammonaemia and similar neurological sequelae. In this condition there is no deficiency of urea-cycle enzymes but a deficiency of urea-cycle substrate, such as ornithine, which results in reduced synthesis of citrulline. Patients are treated with dietary protein restriction and citrulline supplementation, which improves protein tolerance and nutrition but only slightly ameliorates growth retardation. Osteoporosis may be severe in children with this disorder.¹ A child presenting with osteopenia and diagnosed with lysinuric protein intolerance was given large oral doses of citrulline (up to 5.7 g daily). Aside from a substantial increase in protein tolerance, a striking acceleration in linear growth and bone mass was reported.² Lysine deficiency may be implicated in growth retardation,¹ but lysine supplementation may precipitate diarrhoea and malabsorption.² Six patients with lysinuric protein intolerance and receiving oral citrulline were supplemented with oral lysine. Larger lysine doses of 0.55 mmol/kg and 1.1 mmol/kg given consecutively, caused

profuse diarrhoea, but smaller doses of 0.05 mmol/kg, given three times daily (up to a maximum dose of 2.5 mmol) were well tolerated. Plasma lysine concentrations were normalised with no adverse effects on the urea cycle.¹

1. Lukkariinen M, et al. Oral supplementation corrects plasma lysine concentrations in lysinuric protein intolerance. *Metabolism* 2003; **52**: 935–8.
2. Carpenter TO, et al. Lysinuric protein intolerance presenting as childhood osteoporosis: clinical and skeletal response to citrulline therapy. *N Engl J Med* 1985; **312**: 290–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Stimol; **Indon.:** Stimol; **Port.:** Dyrnergum; **Rus.:** Stimol (Стимол); **Spain:** Stimol; **Switz.:** Biostimol.

Multi-ingredient: **Braz.:** Omihepat†; Omitargin; **Fr.:** Epuram†; **Ger.:** Polilevo N†; **Ital.:** Ipoazotal Complex; Ipoazotal†; Polilevo†.

Cod-liver Oil (BAN)

Aceite de hígado de bacalao; Balık yağı; Cod Liver Oil; Csukamá-jolaj; Foie de morue, huile de; Huile de Foie de Morue; lecoris aselli oleum; Kalanmaksajly; Lebertran; Menkiu kepenų taukai; Ol. Morrh.; Óleo de Bacalhau; Oleum Jecoris Aselli; Oleum Morrhuae; Olio di Fegato di Merluzzo; Rybí olej; Torskleverolja. Тресковый Печёночный Жир

CAS — 8001-69-2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn.*, and *US*.

Ph. Eur. 6.2 (Cod-liver Oil (Type A) and Cod-liver Oil (Type B)). Purified fatty oils obtained from the fresh livers of *Gadus morhua* and other species of Gadidae, solid substances being removed by cooling and filtering. The oils contain not less than 600 units (180 micrograms) and not more than 2500 units (750 micrograms) of vitamin A per g and not less than 60 units (1.5 micrograms) and not more than 250 units (6.25 micrograms) of vitamin D₃ (colecalciferol) per g. Authorised antioxidants in concentrations not exceeding those prescribed by the competent authority may be added.

Clear yellowish viscous liquids. Practically insoluble in water; slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Store under an inert gas if no antioxidant is added. Protect from light.

USP 31 (Cod Liver Oil). The partially destearinated fixed oil obtained from the fresh livers of *Gadus morhua* and other species of Gadidae. It contains not less than 600 units (180 micrograms) and not more than 2500 units (750 micrograms) of vitamin A per g and not less than 60 units (1.5 micrograms) and not more than 250 units (6.25 micrograms) of vitamin D per g. It may be flavoured by the addition of not more than 1% of a suitable flavour or a mixture of flavours. A suitable antioxidant may be added.

A thin, oily liquid, having a characteristic, slightly fishy but not rancid odour. Slightly soluble in alcohol; freely soluble in carbon disulfide, in chloroform, in ether, and in ethyl acetate. Store in airtight containers. It may be bottled or packaged in containers from which air has been expelled by the production of a vacuum or by an inert gas.

Profile

Cod-liver oil is a rich source of vitamin D (p.1986) and a good source of vitamin A (p.1971). It also contains several essential fatty acids.

Cod-liver oil dressings or ointment have been advocated to accelerate healing in burns, ulcers, pressure sores, and superficial wounds, but controlled observations have failed to substantiate claims of their value.

Preparations

USP 31: Cod Liver Oil Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Hypol†; **Austria:** Adecaps; Vitapan; **Ger.:** Gelovital; Unguentolan; **Hong Kong:** Scott's Emulsion; **India:** Seaking†; **Ital.:** Dermovitamina; **Pol.:** Letin-Tran; Masec Tranowa; Naturkaps Tran; **Spain:** Aceite Geve Concentrado; **Switz.:** Morrhulan; **Turk.:** Seven Seas Pulse; **Venez.:** North Sea†; Scott Traditional; Supercod.

Multi-ingredient: **Arg.:** Abanta; Atomoderma A-D; Atomoderma Plus; Eryteal; Hipoglos con Hidrocortisona; Klarane Bebe Eryteal; **Austral.:** Covitol; Desitin Nappy Rash Ointment; Hypol; **Austria:** Dermilon; Dermomund; Desitin; Leukichtan; Mirfulan; Nuri-Kapseln; Pudan-Lebertran-Zinksalbe; Vulpuran; **Belg.:** Mitosyl; Newdermig†; Polyseptol; **Braz.:** Blumen†; Calciumvit Infantil†; Hiposan; Oxizinc; Topiglos; **Canad.:** Desitin; **Chile:** Cikalvit; Deltisan; Dulinas†; NeneGLOSS; Pediaidermig†; Vatanal; **Cz.:** Desitin†; **Fr.:** Eryteal†; Halvite†; Magalite; **Ger.:** Dermilon; Desitin; Leukona-Wundsalbe†; Mirfulan; Mirfulan Spray N; Mitosyl N; Zinksalbe; **Gr.:** Fisan-Pate†; Fissan†; **Hong Kong:** Desitin; Scott's Emulsion Orange; **India:** Seaking Plus†; **Indon.:** Co-Q-10; Scott's Emulsion; **Ir.:** Caldease; Morhulin; **Israel:** Desitin; Rekasint; Zincod; **Ital.:** Fosfarsile Junior; Neo-Ustiol; Steril Zeta; Trofo 5; **Mex.:** Bacnuri; Capent; Desitin; Emulsion de Scott; Glossderm; Sutin†; **Norw.:** Aselli; **Pol.:** Dehalid†; Rectosec; Tran z Olejem Wiesolkowym†; Tranvit; **Port.:** Mitosyl; **S.Afr.:** Achromide; Daromide; SB Universal Ointment; Ung. Vermleigh; **Singapore:** Seven Seas Joint-Care High Strength; **Spain:** Avnil; **Switz.:** Kerodermig†; Leucen; Radix†; Unguentolan; Vita-Hexin; **UK:** Artheumacare; Clogar; JointCare Max; M & M; Morhulin; **USA:** A and D Medicated; Caldesene; Clocream; Desitin; Diaper Rash; Dyprotex; **Venez.:** Wampole†.

Copper

Cobre; Cuivre; Cuprum; Koppar; Kupari; Kupfer; Miedz.

Cu = 63.546.
CAS — 7440-50-8.

Pharmacopoeias. *Eur.* (see p.vii) includes Copper for Homeopathic Preparations.

Ph. Eur. 6.2 (Copper for Homeopathic Preparations; Cuprum ad Praeparationes Homeopathicae). A reddish-brown powder. Practically insoluble in water and in alcohol; soluble in hydrochloric acid and in nitric acid.

Calcium Copperedetate

Cuproedetato cálcico. Calcium [ethylenediaminetetra-acetato(4-)-N,N',O,O']copper (II) dihydrate.

$C_{10}H_{12}CaCuN_2O_8 \cdot 2H_2O = 427.9$.

CAS — 66317-91-7 (anhydrous calcium copperedetate).

Pharmacopoeias. In *BP* (Vet).

BP (Vet) 2008 (Calcium Copperedetate). A blue crystalline powder. It contains 9.1 to 9.7% of Ca and 14.4 to 15.3% of Cu. Freely soluble in water, the solution gradually precipitating the tetrahydrate; practically insoluble in alcohol.

Copper Chloride

Cobre, cloruro de; Cupric Chloride; Miedzi chlorek.

$CuCl_2 \cdot 2H_2O = 170.5$.

CAS — 7447-39-4 (anhydrous copper chloride); 10125-13-0 (copper chloride dihydrate).

Pharmacopoeias. In *US*.

USP 31 (Cupric Chloride). Bluish-green, deliquescent crystals. Freely soluble in water; soluble in alcohol; slightly soluble in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Copper Gluconate

Cobre, gluconato de; Copper D-gluconate (1:2); Bis(D-gluconato-O',O'') copper.

$C_{12}H_{22}CuO_{14} = 453.8$.

CAS — 527-09-3.

Pharmacopoeias. In *US*.

Copper Sulfate

Cobre, sulfato de; Copper Sulph. Copper Sulphate; Cuivre (Sulfate de); Cuivre, sulfate de; Cupri sulfas; Cupri Sulphas; Cupric Sulfate; Kopparsulfat; Kupansulfatti; Kupfersulfat; Miedzi(II) siarczan; Réz(II)-szulfát; Sírán mészát; Sulfato de Cobre; Vario sulfatas. Copper (II) sulphate pentahydrate.

$CuSO_4 \cdot 5H_2O = 249.7$.

CAS — 7758-98-7 (anhydrous copper sulfate); 7758-99-8 (copper sulfate pentahydrate).

ATC — V03AB20.

ATC Vet — QV03AB20.

NOTE. Crude copper sulfate is sometimes known as 'blue copper-as', 'blue stone', and 'blue vitriol'.

Pharmacopoeias. In *Eur.* (see p.vii), *US*, and *Viet*.

Eur. and *Viet.* also include anhydrous copper sulfate.

Ph. Eur. 6.2 (Copper Sulphate Pentahydrate). A blue crystalline powder or transparent blue crystals. Freely soluble in water; practically insoluble in alcohol; soluble in methyl alcohol.

Ph. Eur. 6.2 (Copper Sulphate, Anhydrous). A greenish-grey, very hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. Store in airtight containers.

USP 31 (Cupric Sulfate). Deep blue, triclinic crystals, or blue, crystalline granules or powder. It effloresces slowly in dry air. Soluble 1 in 3 of water, 1 in 0.5 of boiling water, 1 in 500 of alcohol, and 1 in 3 of glycerol. Its solutions are acid to litmus. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Treatment

Adverse effects from copper have tended to arise after absorption of the metal from cooking utensils and during dialysis. Ingestion of copper from cooking utensils is associated mainly with hepatotoxicity. Dialysis procedures may supply copper through the water supply or from parts of the equipment and when this happens patients may suffer haemolysis and other haematological reactions, kidney involvement, and hepatotoxicity; the toxicity is generally a result of poor equipment maintenance.

Adverse effects attributed to copper have been reported in women with copper-containing intra-uterine devices. There have been isolated case reports of various effects such as allergy and endometrial changes. However, it is difficult to separate those adverse effects that are due to the device from those due solely to the copper.

The symptoms of Wilson's disease (hepatolenticular degeneration) (see p.1459) are due to an accumulation of copper in various parts of the body.

Copper salts if ingested can produce severe gastrointestinal effects and there may be systemic absorption of copper leading to the effects discussed above. The use of sprays of copper salts in agriculture has been associated with lung changes. Treatment of copper poisoning is symptomatic and may involve the use of a chelating agent to remove any absorbed metal. Dialysis has been tried.