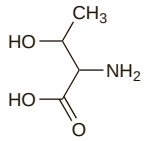
Threonine *(USAN, rINN)*

β-Methylserine; T; Thr; Threonin; Thréonine; L-Threonine; Threoninum; Treoniini; Treonin; Treonina; Treoninas. L-2-Amino-3-hydroxybutyric acid.

Треонин

$C_4H_9NO_3$ = 119.1.

CAS — 72-19-5.



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

Ph. Eur. 6.2 (Threonine). A white or almost white, crystalline powder or colourless crystals. Soluble in water; practically insoluble in alcohol. A 2.5% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 31 (Threonine). White, odourless crystals. Freely soluble in water; insoluble in dehydrated alcohol, in chloroform, and in ether. pH of a 5% solution in water is between 5.0 and 6.5.

Profile

Threonine is an amino acid that is an essential constituent of the diet. It is used as a dietary supplement.

Threonine has been investigated for the treatment of various spastic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Stimolfit.

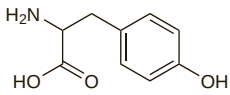
Tyrosine *(USAN, rINN)*

Tirosina; Tirozin; Tirozinas; Tyr; Tyrosiini; Tyrosin; L-Tyrosine; Tyrosinum; Tyrozyna; Y. L-2-Amino-3-(4-hydroxyphenyl)propionic acid.

Тирозин

$C_9H_{11}NO_3$ = 181.2.

CAS — 60-18-4.



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

Ph. Eur. 6.2 (Tyrosine). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Tyrosine). White, odourless crystals or crystalline powder. Very slightly soluble in water; insoluble in alcohol and in ether.

Profile

Tyrosine is an aromatic non-essential amino acid. It is used as a dietary supplement.

Phenylketonuria. Tyrosine was not an effective alternative to a diet low in phenylalanine in patients with phenylketonuria, see under Amino Acid Metabolic Disorders, p.1922.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Aussie Tan Pre-Tan; Bioglan Zellulean with Escin; Tyroseng†; ***India:*** Placentrex; ***Port.:*** Rilastil Dermo Solar.

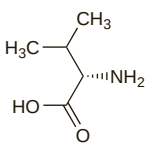
Valine *(USAN, rINN)*

α-Aminoisovaleric Acid; V; Val; Valiini; Valin; Valina; Valinas; L-Valine; Valinum. (*S*)-2-Amino-3-methylbutanoic acid.

Валин

$C_5H_{11}NO_2$ = 117.1.

CAS — 72-18-4.



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

Ph. Eur. 6.2 (Valine). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol. Protect from light.

USP 31 (Valine). White, odourless crystals. Soluble in water; practically insoluble in alcohol, in acetone, and in ether. pH of a 5% solution in water is between 5.5 and 7.0.

Profile

Valine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Revitalose; ***Ger.:*** Bramin-hepa†; Falkamin; ***Ital.:*** Falkamin†; Isobranch; Isoram.

Vitamin A *(USAN)*

Retinol *(BAN, rINN)*; Antixerophthalmic Vitamin; A-vitamiini; A-vitamin; Axerophtholum; Oleovitamin A; Rétinol; Retinolum; Vitamin A Alcohol; Vitaminas A; Vitamine A; Vitaminum A; Witamina A. 15-Apo-β-caroten-15-ol; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraen-1-ol.

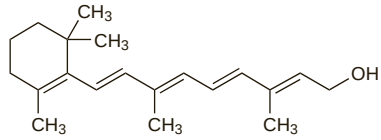
Ретинол

$C_{20}H_{30}O$ = 286.5.

CAS — 68-26-8.

ATC — A11CA01; D10AD02; R01AX02; S01XA02.

ATC Vet — QA11CA01; QD10AD02; QR01AX02; QS01XA02.



Description. Vitamin A is generally used in the form of esters, such as the acetate, palmitate, and propionate.

Vitamin A Acetate. Retinol Acetate; Retinyl Acetate; $C_{22}H_{32}O_2$ = 328.5; CAS — 127-47-9

Vitamin A Palmitate. Retinol Palmitate; Retinyl Palmitate; $C_{36}H_{60}O_2$ = 524.9; CAS — 79-81-2

Vitamin A Propionate. Retinol Propionate; Retinyl Propionate; $C_{23}H_{34}O_2$ = 342.5; CAS — 7069-42-3.

Pharmacopoeias. In *Eur.* (see p.vii), *US*, and *Viet.*, which permit retinol or its esters.

Chin. includes a monograph for the acetate. *Jpn* includes monographs for the acetate and the palmitate.

Br. includes a monograph for a natural ester concentrate.

Eur. also includes monographs for synthetic concentrates in an oily form, a powder form, and a solubilisate/emulsion.

Int. includes an oily concentrated form.

The BP 2008 states that the term 'Retinol' is used within BP titles for preparations containing synthetic ester(s) and the term 'Vitamin A' within the BP title for the preparation containing material of natural origin.

Ph. Eur. 6.2 (Vitamin A). Under the name Vitamin A are included a number of substances of very similar structure (including (*Z*)-isomers) found in animal tissues and possessing similar activity. The principal and biologically most active substance is all-(*E*) retinol.

Vitamin A is generally used in the form of esters such as the acetate, propionate, and palmitate. Synthetic retinol ester refers to an ester (acetate, propionate, or palmitate) or a mixture of synthetic retinol esters.

Retinol acetate occurs as pale yellow crystals. M.p. about 60°; once melted it tends to yield a supercooled melt. Retinol propionate occurs as a reddish-brown oily liquid. Retinol palmitate occurs as a fat-like, light yellow solid, or as a yellow oily liquid, if melted. M.p. about 26°. All retinol esters are practically insoluble in water; soluble or partly soluble in dehydrated alcohol; miscible with organic solvents.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used should be protected by an atmosphere of inert gas.

Ph. Eur. 6.2 (Vitamin A Concentrate (Oily Form), Synthetic; Vitaminum A Densatum Oleosum; Synthetic Retinol Concentrate (Oily Form) BP 2008). It is prepared from synthetic retinol ester as is or by dilution with a suitable vegetable oil. It contains not less than 500 000 units of vitamin A per g. It is a yellow or brownish-yellow, oily liquid; practically insoluble in water; soluble or partly soluble in dehydrated alcohol; miscible with organic solvents. Partial crystallisation may occur in highly concentrated solutions.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

Ph. Eur. 6.2 (Vitamin A Concentrate (Powder Form), Synthetic; Vitaminum A Pulvis; Synthetic Retinol Concentrate (Powder Form) BP 2008). It is obtained by dispersing a synthetic retinol ester in a matrix of gelatin or acacia or other suitable material. It contains not less than 250 000 units of vitamin A per g. It is a yellowish powder usually in the form of particles of almost uniform size. Practically insoluble in water or may swell or form an emulsion, depending on formulation.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

Ph. Eur. 6.2 (Vitamin A Concentrate (Solubilisate/Emulsion), Synthetic; Vitaminum A in Aqua Dispergibile; Synthetic Retinol Concentrate, Solubilisate/Emulsion BP 2008). It is a liquid form (water is generally used as solvent) of synthetic retinol ester and a suitable solubiliser. It contains not less than 100 000 units of vitamin A per g. It is a yellow or yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperatures or take the form of a gel. A mixture of 1 g with 10 mL of water previously warmed to 50° gives after cooling to 20°, a uniform, slightly opalescent and slightly yellow dispersion.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

BP 2008 (Natural Vitamin A Ester Concentrate). It consists of a natural ester or a mixture of natural esters of retinol or of a solution of the ester or mixture of esters in arachis oil or other suitable vegetable oil. It contains not less than 485 000 units of vitamin A per g. It is a yellow oil or a mixture of oil and crystalline material, with a faint odour. Practically insoluble in water; soluble or partly soluble in alcohol; miscible with chloroform, with ether, and with petroleum spirit. Store in airtight containers at 8° to 15°. Protect from light.

USP 31 (Vitamin A). It may consist of retinol or its esters formed from edible fatty acids, principally acetic and palmitic acids. In liquid form, it is a light yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. It may be practically odourless or may have a mild fishy odour but no rancid odour or taste. It is unstable in air and light. In liquid form, it is insoluble in water and in glycerol; soluble in dehydrated alcohol and in vegetable oils; very soluble in chloroform and in ether. In solid form, may be dispersible in water. Store in airtight containers, preferably under an atmosphere of inert gas. Protect from light.

Units

The International Standards for vitamin A and for provitamin A were discontinued in 1954 and 1956 respectively but the International units for these substances have continued to be widely used. In 1960–1, the WHO Expert Committee on Biological Standardization stated that the International unit for vitamin A is equivalent to the activity of 0.000344 mg of pure all-*trans* vitamin A acetate and the International unit for provitamin A is equivalent to the activity of 0.0006 mg of pure all-*trans* β-carotene.

The activity of one International unit is contained in 0.0003 mg of all-*trans* retinol, in 0.00055 mg of all-*trans* retinol palmitate, and in 0.000359 mg of all-*trans* retinol propionate.

The USP 31 defines 1 USP unit as equal to the biological activity of 0.0003 mg of the all-*trans* isomer of retinol, and is equivalent to the International unit.

Vitamin A activity in foods is currently expressed in terms of retinol equivalents: 1 retinol equivalent is defined as 1 microgram of all-*trans* retinol, 6 micrograms of all-*trans* beta carotene, or 12 micrograms of other provitamin A carotenoids.

Adverse Effects and Precautions

The use of excessive amounts of vitamin A substances over long periods can lead to toxicity. Rarely, acute toxicity may also occur with very high doses.

- Hypervitaminosis A (chronic toxicity) is characterised by fatigue, irritability, anorexia and loss of weight, vomiting and other gastrointestinal disturbances, low-grade fever, hepatomegaly, skin changes (yellowing, dryness, sensitivity to sunlight), pruritus, alopecia, dry hair, cracking and bleeding lips, anaemia, headache, hypercalcaemia, subcutaneous swelling, nocturia, and pains in bones and joints. Symptoms of chronic toxicity may also include raised intracranial pressure and papilloedema mimicking brain tumours, and visual disturbances which

may be severe. Symptoms usually clear on withdrawal of vitamin A, but in children premature closure of the epiphyses of the long bones may result in arrested bone growth.

- Acute vitamin A intoxication is characterised by sedation, dizziness, confusion, diarrhoea and vomiting, sore mouth, bleeding gums, desquamation, and increased intracranial pressure (resulting in bulging fontanelle in infants or severe headache in adults). Hepatomegaly and visual disturbances may occur; irritability may be severe.

Hypervitaminosis A does not appear to be a problem with large doses of carotenoids (see Pharmacokinetics under Betacarotene, p.1931).

Enhanced susceptibility to the effects of vitamin A may be seen in children and in patients with liver disease.

Excessive doses of vitamin A should be avoided in pregnancy because of potential teratogenic effects; for further details see Pregnancy, below.

Gastrointestinal absorption of vitamin A may be impaired in cholestatic jaundice and fat-malabsorption conditions.

Benign intracranial hypertension. High doses of vitamin A cause increased intracranial pressure, and, in infants, this is manifested as bulging of the fontanelle. In one study,[1] 11.5% of infants receiving 3 doses of 50 000 units of vitamin A at monthly intervals had bulging fontanelle, compared with 1% of infants receiving placebo. The bulging lasted between 24 and 72 hours and subsided without treatment,[1] and did not appear to be associated with any physical or developmental abnormalities on long-term follow-up.[2] In another study in neonates, bulging fontanelle occurred in 4.6% of recipients of vitamin A 50 000 units and 2.7% of placebo recipients 24 hours after the dose.[3] In contrast, less than 1% of infants given 3 doses of 25 000 units of vitamin A at monthly intervals had bulging fontanelle in a further study.[4]

1. de Francisco A, *et al.* Acute toxicity of vitamin A given with vaccines in infancy. *Lancet* 1993; **342:** 526–7.
2. van Dillen J, *et al.* Long-term effect of vitamin A with vaccines. *Lancet* 1996; **347:** 1705.
3. Agoestina T, *et al.* Safety of one 52 micromol (50 000 IU) oral dose of vitamin A administered to neonates. *Bull WHO* 1994; **72:** 859–68.
4. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998; **352:** 1257–63. Correction. *ibid.* 1999; **353:** 154.

Carcinogenicity. For mention of the *increased* risk of lung cancer in high-risk individuals receiving betacarotene and vitamin A, when compared with placebo, in a study investigating vitamins in lung cancer prevention, see Prophylaxis of Malignant Neoplasms, p.1927.

Effects on the blood. Normochromic macrocytic anaemia developed in a patient who had been receiving vitamin A 150 000 units daily by mouth for several months.[1] The patient's haemoglobin returned to normal when vitamin A was stopped, and the accompanying symptoms of perioral dermatitis and glossitis also disappeared. Similarly, normochromic normocytic anaemia and thrombocytopenia in an infant given 62 000 units daily for 80 days, resolved on stopping vitamin A.[2] In contrast, vitamin A has been reported to have a beneficial effect on anaemia, see under Deficiency states, below.

1. White JM. Vitamin-A-induced anaemia. *Lancet* 1984; **ii:** 573.
2. Perrotta S, *et al.* Infant hypervitaminosis A causes severe anemia and thrombocytopenia: evidence of a retinol-dependent bone marrow cell growth inhibition. *Blood* 2002; **99:** 2017–22.

Effects on bone. Excessive dietary intake of vitamin A may be associated with osteoporosis. In an epidemiological study,[1] a dietary intake of retinol greater than 1500 micrograms daily (5000 units) doubled the risk of hip fracture compared with an intake of less than 500 micrograms daily (about 1670 units) in women (odds ratio, 2.1; 95% confidence interval 1.1 to 4.0). These data were confirmed by the Nurses' Health Study,[2] which found that postmenopausal women with the highest vitamin A and retinol intakes were at increased risk for hip fracture, irrespective of whether the intakes were from food plus supplements, or food alone. Women with daily retinol intakes of more than 1500 micrograms had a relative risk for hip fracture of 1.64 compared with those consuming less than 500 micrograms daily. Betacarotene intake, however, did not correlate significantly with an increased risk of fracture. A large cohort study[3] of men found that the overall risk of any fracture, including hip fractures, was substantially increased among men with the highest concentrations of serum retinol; there was no association between serum betacarotene levels and the risk of fracture. Subsequently, routine supplementation and the fortification of food with vitamin A in western countries has been questioned.[4] A report[5] from the UK Government's Scientific Advisory Committee on Nutrition cautions against the intake of more than 1.5 mg of vitamin A daily in those at increased risk of osteoporosis, such as postmenopausal women and the elderly. However, results from a cohort study in the elderly[6] suggest a U-shaped dose relationship, in that both high and low intakes of vitamin A were associated with reduced bone mineral density, and another study[7] in women aged between 50 and 74 years, found both high and low serum vitamin A concentrations to be associated with an increased risk of hip fracture.

1. Melhus H, *et al.* Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Intern Med* 1998; **129:** 770–8.
2. Feskanich D, *et al.* Vitamin A intake and hip fractures among postmenopausal women. *JAMA* 2002; **287:** 47–54.
3. Michaëlsson K, *et al.* Serum retinol levels and the risk of fracture. *N Engl J Med* 2003; **348:** 287–94.
4. Lips P. Hypervitaminosis A and fractures. *N Engl J Med* 2003; **348:** 347–9.
5. Scientific Advisory Committee on Nutrition. *Review of dietary advice on vitamin A.* London: The Stationery Office, 2005. Also available at: http://www.sacn.gov.uk/pdfs/sacn_vita_report.pdf (accessed 21/07/08)
6. Promislow JHE, *et al.* Retinol intake and bone mineral density in the elderly: the Rancho Bernardo Study. *J Bone Miner Res* 2002; **17:** 1349–58.
7. Opotowsky AR, Bilezikian JP. Serum vitamin A concentration and the risk of hip fracture among women 50 to 74 years old in the United States: a prospective analysis of the NHANES I Follow-up Study. *Am J Med* 2004; **117:** 169–74.

Effects on the immune system. Vitamin A deficiency is generally associated with impaired immunity, and treatment of deficiency results in reductions in morbidity and mortality from a number of infectious diseases (see under Deficiency States, below). However, a few studies have shown increased prevalence of diarrhoea and/or respiratory-tract infections with high doses of vitamin A. There is a possibility that high single doses of vitamin A may temporarily attenuate the immune response in non-deficient children.[1] For the effect of high-dose vitamin A supplements on the response to measles vaccine in some studies, see p.2222.

1. Anonymous. Childhood morbidity, immunity and micronutrients. *WHO Drug Inf* 1996; **10:** 12–16.

Effects on the liver. Vitamin A is stored in the Dissë space of liver cells and excessive dosage can lead to fibrosis and obstruction of sinusoidal blood flow, causing non-cirrhotic portal hypertension and hepatocellular dysfunction.[1] Although hepatotoxicity has typically been reported with habitual ingestion of doses of vitamin A greater than 50 000 units daily, a case of severe hepatic fibrosis, with jaundice and hepatomegaly, has been reported in a patient who had been taking 25 000 units daily for at least 6 years in a multivitamin supplement.[2]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Kowalski TE, *et al.* Vitamin A hepatotoxicity: a cautionary note regarding 25,000 IU supplements. *Am J Med* 1994; **97:** 523–8.

Effects on mortality. Vitamin A supplementation has been reported to have beneficial effects on childhood mortality, especially in developing countries, see Deficiency States, below *et seq.* However, a systematic review of antoxidant supplementation in adults concluded that vitamin A either singly or with other antoxidants increased mortality.[1]

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Hypersensitivity. Local inflammatory reactions and severe anaphylactoid reactions have occurred in patients receiving vitamin A injections, and are usually attributed to solubilisers such as polyoxyl castor oils (p.1918), and, less commonly, polysorbates (p.1919).

A case of cutaneous hypersensitivity to retinol palmitate itself has been described.[1]

1. Shelley WB, *et al.* Hypersensitivity to retinol palmitate injection. *BMJ* 1995; **311:** 232.

Overdosage. Although no clinical manifestations of toxicity were seen in 3 boys who ingested large amounts of vitamin A, their serum retinol concentrations continued to rise over about 3 weeks, and took several months to normalise; the authors cautioned that the use of chewable vitamins resembling confectionery may increase the risk of overdose in children.[1]

1. Lam HS, *et al.* Risk of vitamin A toxicity from candy-like chewable vitamin supplements for children. *Pediatrics* 2006; **118:** 820–4.

Pregnancy. The fact that synthetic vitamin A derivatives such as isotretinoin are teratogenic (p.1601) has prompted concern about the potential teratogenicity of high doses of vitamin A.

A prospective cohort study found that a total daily intake of vitamin A from all sources of greater than 15 000 units during early pregnancy was associated with a significantly increased risk of birth defects of structures arising from the cranial neural crest.[1] When vitamin A intake from supplements was analysed separately, an apparent vitamin A threshold dose for the development of birth defects of 10 000 units daily was suggested. However, this study has been criticised[2,3] and some suggest the data allows for a higher threshold dose.[3] A further study found no significant difference in birth defect rates between women consuming greater than 8000 or 10 000 units of vitamin A daily in the period around conception (as supplements and fortified cereals) and those consuming less than 5000 units daily.[4]

After earlier case reports in the USA suggesting that large doses of vitamin A (equivalent to about ten times the daily recommended dietary allowance of 2250 units) taken in early pregnancy may cause birth defects, the UK Chief Medical Officer cautioned women against the use of vitamin A supplements except under medical supervision.[5] Additionally, advice was given that liver or liver products should not be eaten because high concentrations of vitamin A had been detected in some samples of animal liver. However, others thought that the avoidance of liver or liver products might result in inadequate nutrition in some and that a less alarmist view might have been to suggest a limitation on intake rather than total prohibition.[6,7]

The American College of Obstetricians and Gynecologists has recommended that women who are pregnant or planning pregnancy should ensure that any vitamin supplements they take contain a daily dose of vitamin A of no more than 5000 units.[8] The Australian Adverse Drug Reactions Advisory Committee has advised women in this category to avoid vitamin A supplements and to not exceed the recommended daily allowance of 2500 units from all sources.[9]

1. Rothman KJ, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1995; **333:** 1369–73.
2. Werler MM, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1996; **334:** 1195–6.
3. Watkins M, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1996; **334:** 1196.
4. Mills JL, *et al.* Vitamin A and birth defects. *Am J Obstet Gynecol* 1997; **177:** 31–6.
5. Department of Health. *Women cautioned: watch your vitamin A intake*. London: Department of Health, 1990 (18 October).
6. Nelson M. Vitamin A, liver consumption, and risk of birth defects. *BMJ* 1990; **301:** 1176.
7. Sanders TAB. Vitamin A and pregnancy. *Lancet* 1990; **336:** 1375.
8. American College of Obstetricians and Gynecologists. ACOG committee opinion: vitamin A supplementation during pregnancy. Number 196, January 1998 (replaces No. 157, September 1995). *Int J Gynaecol Obstet* 1998; **61:** 205–6.
9. Adverse Drug Reactions Advisory Committee (ADRAC). Vitamin A and birth defects. *Aust Adverse Drug React Bull* 1996; **15:** 14–15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9611.htm (accessed 21/07/08)

Interactions

Absorption of vitamin A from the gastrointestinal tract may be reduced by the presence of neomycin, colestyramine, or liquid paraffin.

There is an increased risk of hypervitaminosis A if vitamin A is given with synthetic retinoids such as acitretin, isotretinoin, and tretinoin.

There is conflicting evidence regarding the effect of vitamin A on the response to measles vaccine (see p.2222).

Pharmacokinetics

Vitamin A substances are readily absorbed from the gastrointestinal tract but absorption may be reduced in the presence of fat malabsorption, low protein intake, or impaired liver or pancreatic function. Vitamin A esters are hydrolysed by pancreatic enzymes to retinol, which is then absorbed and re-esterified. Some retinol is stored in the liver. It is released from the liver bound to a specific α_1-globulin (retinol-binding protein) in the blood. The retinol not stored in the liver undergoes glucuronide conjugation and subsequent oxidation to retinal and retinoic acid; these and other metabolites are excreted in urine and faeces. Vitamin A does not readily diffuse across the placenta (but see Pregnancy, above), but is present in breast milk.

◊ References.

1. Hartmann D, *et al.* Pharmacokinetic modelling of the plasma concentration-time profile of the vitamin retinyl palmitate following intramuscular administration. *Biopharm Drug Dispos* 1990; **11:** 689–700.
2. Reinersdorff DV, *et al.* Plasma kinetics of vitamin A in humans after a single oral dose of [8,9,19-] retinyl palmitate. *J Lipid Res* 1996; **37:** 1875–85.
3. Harrison EH, Hussain MM. Mechanisms involved in the intestinal digestion and absorption of dietary vitamin A. *J Nutr* 2001; **131:** 1405–8.

Human Requirements

Dietary vitamin A is derived from 2 sources, *preformed retinoids* from animal sources such as liver, kidney, dairy produce, and eggs (fish-liver oils are the most concentrated natural source), and *provitamin carotenoids* which can be obtained from many plants; the latter are converted to retinol in the body but are less effectively utilised. Carotenes (α, β, and γ) are major sources and of these, β-carotene (betacarotene—see

p.1930) has the highest vitamin A activity and is the most plentiful in food. Variable amounts of β-carotenes are found in carrots and dark green or yellow vegetables. Red palm oil is a good source of α- and β-carotenes.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published[1] for vitamin A and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women (but see Pregnancy, above). In the UK the reference nutrient intake (RNI) for adult males and females is 700 and 600 micrograms retinol equivalents (about 2330 and 2000 units) daily, respectively and the estimated average requirement (EAR) is 500 and 400 micrograms retinol equivalents (about 1660 and 1330 units) daily, respectively. This UK report[1] also highlighted the toxicity associated with large doses of vitamin A and recommended that regular intakes should not exceed 9000 micrograms (30 000 units) daily in adult men and 7500 micrograms (25 000 units) daily in adult women. (A later report[3] was unable to establish a safe upper level for vitamin A intake, but considered that total intakes above 1500 micrograms retinol equivalents daily might be inappropriate.) Figures were also given in the earlier report for infants and children who were said to be more sensitive to the effects of vitamin A. These limits did not apply to therapeutic doses of vitamin A used under medical supervision.[1] In pregnancy the RNI is 700 micrograms retinol equivalents (2330 units) daily and in nursing mothers 950 micrograms (3160 units) daily. In the USA the RDA for adults is 900 micrograms daily for men and 700 micrograms daily for women.[2] The tolerable upper intake level is 3000 micrograms daily.

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. http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. 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 06/01/06)

Uses and Administration

Vitamin A, a fat-soluble vitamin, is essential for growth, for the development and maintenance of epithelial tissue, and for vision, particularly in dim light. Vitamin A deficiency develops when the dietary intake is inadequate and is seen more frequently in young children than in adults. It is rare in developed countries but remains a major problem in many developing countries. Prolonged deficiency leads to xerophthalmia or 'dry eye', the initial symptom of which is night blindness which may progress to severe eye lesions and blindness. Other symptoms include changes in the skin and mucous membranes.

Vitamin A is used in the treatment and prevention of vitamin A deficiency. It may be given orally in an oil- or water-based form, the oil-based generally being the preferred type. It can also be given by intramuscular injection of a water-miscible form; oil-miscible preparations of vitamin A are poorly absorbed from injection sites after intramuscular injection and are not usually given by this route. For further details concerning vitamin A supplementation, including doses for the treatment and prophylaxis of xerophthalmia, see below.

Vitamin A supplements are often given to patients with primary biliary cirrhosis or chronic cholestatic liver disease as deficiencies are common in these disorders. An intramuscular dose of 100 000 units every 2 to 4 months has been suggested.

Vitamins A and D have been used together in creams or ointments in the treatment of minor skin disorders including abrasions. Vitamin A has also been used alone to treat various skin disorders including acne and psoriasis. It has been tried in patients with retinitis pigmentosa to retard the decline in retinal function.

Deficiency states. Vitamin A deficiency is relatively rare in developed countries and is usually only seen in certain medical conditions such as biliary cirrhosis or cholestatic jaundice. However, it is a continuing problem in many developing countries and children appear to be particularly vulnerable.

In **developing countries** where dietary intake is often less than desirable, infections such as measles, acute respiratory diseases, and diarrhoea can be major precipitating factors of vitamin A deficiency. Thus WHO have targeted elimination of vitamin A deficiency as an important strategy in child health,[1,2] and as part of the Expanded Programme on Immunization. They recommend the use of vitamin A supplements in the treatment of vitamin A deficiency and to prevent vitamin A deficiency where the periodic use of supplements is determined to be the most feasible and effective method of improving vitamin A status.

- In *universal distribution programmes*,[2,3] supplemental doses are given to all children up to the age of 5 at a dose of 200 000 units every 4 to 6 months, with infants between the ages of 6 and 12 months receiving half this dose. Infants aged less than 6 months may receive 50 000 units if they are not breast fed or if they are breast fed and their mothers have not received supplemental vitamin A. If clinical signs of vitamin A deficiency are evident at the time of routine supplementation, treatment should be given as described under Xerophthalmia, below. Mothers should receive 200 000 units within 6 weeks of delivery of a child.
- *Targeted distribution programmes* involve vitamin A supplementation to children and pregnant women in specific high-risk areas.[2] Doses used in children are similar to those used in universal programmes, but doses used in pregnant women should not exceed 10 000 units daily, or 25 000 units weekly.[2]

A number of studies have indicated that general supplementation with vitamin A decreases both mortality rates and morbidity among children in developing countries with a high prevalence of vitamin A deficiency.[4-7] Although not all studies have confirmed these findings,[8,9] two meta-analyses concur that the effect is likely to be genuine especially as regards measles infection,[10,11] (see Measles, below) and researchers and commentators have agreed that overall improvement of vitamin A status is worthwhile and necessary.[12-14] A study in children given half the dose of vitamin A recommended by WHO found that it provided equally good or better protection against mortality, but not against morbidity.[15] Supplementation with vitamin A 23 300 units weekly, or the equivalent amount of betacarotene, in women of child-bearing age reduced pregnancy-related mortality.[16] Some studies have evaluated mortality specifically in infants less than 6 months of age. In one study there was no overall benefit on early infant mortality with a tendency for the relative risk of mortality to increase with improved nutritional status,[17] whereas others reported decreases in mortality at 6 months[18] and 1 year[19] of age. A further study found no sustained benefit of vitamin A supplements on vitamin A status or morbidity beyond the age of 6 months, in infants receiving supplements with immunisation at 6, 10, and 14 weeks.[20] A study in vitamin-A-deficient children has demonstrated abnormalities in T-cell subsets which are corrected by vitamin A supplementation,[21] and it has been proposed that the apparent effects of vitamin A on morbidity and mortality may be due to modulation of immune function (see also Effects on the Immune System, above).

In **other countries** in which vitamin A deficiency is not widespread some form of supplementation may still be considered. Preterm infants have low vitamin A status at birth, which may increase their risk of developing chronic lung disease.[22] A meta-analysis of studies in low birth-weight infants found that vitamin A supplementation was associated with a reduced requirement for oxygen at 36 weeks postmenstrual age.[22] While studies of vitamin A supplementation to prevent chronic lung disease in very low birth-weight infants have had conflicting results,[23,24] some have commented that differences in patient population, postnatal therapies, and dosage of vitamin A could explain these discrepancies, and consider optimal supplementation necessary.[25] Others have called for further studies in preterm infants to define optimal dosage and mode of delivery of vitamin A; research should include quantification of hepatic stores, assessment of retinal function, and long-term clinical outcome.[26]

1. Potter AR. Reducing vitamin A deficiency: could save the eyesight and lives of countless children. *BMJ* 1997; **314:** 317–18.
2. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*. 2nd ed. Geneva: WHO, 1997.
3. WHO. Integration of vitamin A supplementation with immunization. *Wkly Epidem Rec* 1999; **74:** 1–6.
4. Rahmathullah L, *et al.* Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; **323:** 929–35.
5. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
6. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.
7. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.
8. Herrera MG, *et al.* Vitamin A supplementation and child survival. *Lancet* 1992; **340:** 267–71.
9. Gupta P, Indrayan A. Effect of vitamin A supplementation on childhood morbidity and mortality: critical review of Indian studies. *Indian Pediatr* 2002; **39:** 1099–1118.
10. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; **306:** 366–70.
11. Fawzi WW, *et al.* Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993; **269:** 898–903.
12. Anonymous. Vitamin A and malnutrition/infection complex in developing countries. *Lancet* 1990; **336:** 1349–51.
13. Humphrey JH, Rice AL. Vitamin A supplementation of young infants. *Lancet* 2000; **356:** 422–4.
14. Villamor E, Fawzi WW. Vitamin A supplementation: implications for morbidity and mortality in children. *J Infect Dis* 2000; **182** (suppl): S122–S133.
15. Benn CS, *et al.* Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. *BMJ* 2005; **331:** 1428–32.
16. West KP, *et al.* Double blind, cluster randomised trial of low dose supplementation with vitamin A or β carotene on mortality related to pregnancy in Nepal. *BMJ* 1999; **318:** 570–5. Correction. *ibid.*; 1386.
17. West KP, *et al.* Mortality of infants <6 mo of age supplemented with vitamin A: a randomized double-masked trial in Nepal. *Am J Clin Nutr* 1995; **62:** 143–8.
18. Rahmathullah L, *et al.* Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India. *BMJ* 2003; **327:** 254–7.
19. Humphrey JH, *et al.* Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *J Pediatr* 1996; **128:** 489–96.
20. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998; **352:** 1257–63. Correction. *ibid.* 1999; **353:** 154.
21. Semba RD, *et al.* Abnormal T-cell subset proportions in vitamin-A-deficient children. *Lancet* 1993; **341:** 5–8.
22. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/07/08).
23. Tyson JE, *et al.* Vitamin A supplementation for extremely-low-birth-weight infants. *N Engl J Med* 1999; **340:** 1962–8.
24. Wardle SP, *et al.* Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F9–F13.
25. Shenai JP. Vitamin A supplementation in very low birth weight neonates: rationale and evidence. *Pediatrics* 1999; **104:** 1369–74.
26. Mactier H, Weaver LT. Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F103–F108.

ANAEMIA. A study among pregnant Indonesian women with nutritional anaemia (see Iron-Deficiency Anaemia, p.1951) found a beneficial effect for vitamin A on haemoglobin when given with iron supplementation.[1] Similarly, in anaemic children given iron,[2] or adolescents given iron plus folic acid,[3] greater improvements in haemoglobin concentrations were seen with addition of vitamin A to supplementation. Vitamin A is considered essential for haematopoiesis; it has been suggested that vitamin A is required for the mobilisation and utilisation of iron for haemoglobin synthesis.[4] However, there are reports of anaemia caused by vitamin A supplementation, see Effects on the Blood, above.

1. Suharno D, *et al.* Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993; **342:** 1325–8.
2. Mwanri L, *et al.* Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. *J Nutr* 2000; **130:** 2691–6.
3. Ahmed F, *et al.* Concomitant supplemental vitamin A enhances the response to weekly supplemental iron and folic acid in anemic teenagers in urban Bangladesh. *Am J Clin Nutr* 2001; **74:** 108–15.
4. van den Broek N. Anaemia and micronutrient deficiencies. *Br Med Bull* 2003; **67:** 149–60.

DIARRHOEA. Although oral rehydration therapy remains the mainstay of the management of diarrhoea (p.1694) once it develops, it has been suggested that vitamin A supplementation may be of use in reducing the incidence and mortality of diarrhoea during childhood. Several large mortality studies reported that vitamin A supplementation was associated with reduced mortality attributed to diarrhoea,[1-3] although another did not.[4] The effect on morbidity from diarrhoea is even less clear. A reduction in the severity, but not the incidence, of diarrhoea has been noted in two studies.[5,6] However, in one study in children with subclinical vitamin A deficiency, there was an increased prevalence of diarrhoea for 2 weeks after vitamin A supplementation,[7] and in another study, vitamin A increased the incidence of diarrhoea in children aged less than 30 months.[8] A meta-analysis[9] concluded that vitamin A supplementation has no consistent overall protective effect on the incidence of diarrhoea. While severity was not examined, they noted that the decrease in diarrhoea mortality rates but not incidence can be reconciled if vitamin A reduces diarrhoea severity and not susceptibility to infection. This is possibly supported by a study that found that a single high-dose vitamin A supplement, given with standard antibacterial treatment, reduced the severity of acute shigellosis in children in Bangladesh.[10] One group[11] proposed that the inconsistent findings on morbidity of vitamin A supplementation may be due to co-existing micronutrient deficiencies, such as zinc deficiency, that affect the bioavailability of vitamin A. They found combined zinc and vitamin A supplementation to be more effective in reducing persistent diarrhoea and dysentery than either zinc or vitamin A alone (see Vitamin A Deficiency, under Zinc, p.2001).

1. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
2. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.
3. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.

4. Vijayaraghavan K, *et al.* Effect of massive dose of vitamin A on morbidity and mortality in Indian children. *Lancet* 1990; **336:** 1342–5.
5. Barreto ML, *et al.* Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 1994; **344:** 228–31.
6. Bhandari N, *et al.* Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *BMJ* 1994; **309:** 1404–7.
7. Stansfield SK, *et al.* Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; **342:** 578–82.
8. Dibley MJ, *et al.* Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; **126:** 434–42.
9. Grotto I, *et al.* Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003; **142:** 297–304.
10. Hossain S, *et al.* Single dose vitamin A treatment in acute shigellosis in Bangladeshi children: randomised double blind controlled trial. *BMJ* 1998; **316:** 422–6.
11. Rahman MM, *et al.* Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; **323:** 314–18.

HIV INFECTION AND AIDS. A study in Malawi found that the rates of vertical transmission of HIV infection (birth of seropositive infants to seropositive mothers) were inversely related to maternal vitamin A status;[1] vitamin A deficiency during pregnancy was associated with a threefold to fourfold increased risk of mother-to-child transmission of HIV. This was not incompatible with the role of vitamin A in immunity and maintenance of mucosal surfaces, and since both HIV infection and pregnancy are risk factors for vitamin A deficiency, it was suggested that nutritional intervention to reduce vitamin A deficiency might help combat mother-to-child transmission. A South African study[2] found, in contrast, that supplementing HIV-infected pregnant women with vitamin A and betacarotene did not reduce the overall risk of vertical transmission to neonates. Supplementation did reduce the incidence of preterm births, and among these neonates, risk of perinatal HIV transmission was lower in those whose mothers had been supplemented. Vitamin A supplementation actually increased the risk of HIV transmission through breast feeding, with no effect on mortality at 24 months, in a Tanzanian trial.[3] Yet another study,[4] again in Tanzania, for which vertical transmission data were not available, found no evidence of an effect of vitamin A on birth outcomes in HIV-infected women and the authors pointed out that serum concentrations of vitamin A might be a marker of the stage of HIV disease rather than being causally related to outcome. The study did however find that multivitamin supplements reduced the risk of low birth-weight and size for age, and of premature birth, in the offspring of these women.[4] Interestingly, another trial in Tanzania found little difference between vitamin A supplementation and placebo on the progression of HIV disease and mortality. Multivitamin (excluding vitamin A) supplementation delayed disease progression and was associated with decreased mortality; addition of vitamin A to the multivitamin regimen reduced this benefit.[5] This is in contrast to 2 studies in Tanzania[6] and Uganda,[7] which found that vitamin A supplementation decreased mortality in children infected with HIV; however these results were not considered generalisable to communities with access to better healthcare and nutrition.

A systematic review and meta-analysis,[8] which included some of these conflicting trials, did not support the use of vitamin A supplementation to reduce the risk of vertical transmission and concluded that it may in fact increase the risk. Maternal vitamin A supplementation was not considered to decrease childhood mortality at 1 year. In addition, multivitamin supplementation was considered to have no effect on reduction of childhood mortality at 1 year, nor on prevention of preterm delivery.

Means of reducing the risk of HIV infection in neonates are discussed under HIV Infection Prophylaxis, p.858.

1. Semba RD, *et al.* Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet* 1994; **343:** 1593–7.
2. Coutsoudis A, *et al.* Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. *AIDS* 1999; **13:** 1517–24.
3. Fawzi WW, *et al.* Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS* 2002; **16:** 1935–44.
4. Fawzi WW, *et al.* Randomised trial of effects of vitamin supplements on pregnancy outcomes and T-cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998; **351:** 1477–82.
5. Fawzi WW, *et al.* A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004; **351:** 23–32.
6. Fawzi WW, *et al.* A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. *Pediatr Infect Dis J* 1999; **18:** 127–33.
7. Semba RD, *et al.* Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: a controlled clinical trial. *Nutrition* 2005; **21:** 25–31.
8. Mills EJ, *et al.* Vitamin supplementation for prevention of mother-to-child transmission of HIV and pre-term delivery: a systematic review of RCTs including more than 2800 women. *AIDS Res Ther* 2005; **2:** 4.

MEASLES. Vitamin A supplementation has an important role in the prevention of complications from measles.[1,2] Two studies specifically addressing vitamin A status and measles have found that complications such as pneumonia and diarrhoea were less common in children who had received supplements at the time of diagnosis than in those given a placebo.[3,4] WHO has recommended treating children in populations where vitamin A deficiency is common with high-dose vitamin A supplements during episodes of measles as follows:[5]

- all children over 12 months of age—200 000 units
- those between 6 and 12 months of age—100 000 units
- infants less than 6 months of age—50 000 units

Doses are given on 2 consecutive days and followed by a third dose at least 2 weeks later.

Studies in the USA have indicated that even among well-nourished children from a developed country, vitamin A deficiency in measles patients is not uncommon,[6,7] and vitamin A supplementation needs to be considered in children at risk.[8]

1. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; **306:** 366–70.
2. Fawzi WW, *et al.* Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993; **269:** 898–903.
3. Barclay AJG, *et al.* Vitamin A supplements and mortality related to measles: a randomised clinical trial. *BMJ* 1987; **294:** 294–6.
4. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990; **323:** 160–4.
5. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*. 2nd ed. Geneva: WHO, 1997.
6. Arrieta AC, *et al.* Vitamin A levels in children with measles in Long Beach, California. *J Pediatr* 1992; **121:** 75–8.
7. Butler JC, *et al.* Measles severity and serum retinol (vitamin A) concentration among children in the United States. *Pediatrics* 1993; **91:** 1176–81.
8. Committee on Infectious Diseases of the American Academy of Pediatrics. Vitamin A treatment of measles. *Pediatrics* 1993; **91:** 1014–15.

PREMATURITY. The fetus accumulates vitamin A in the third trimester, and most premature infants have low plasma vitamin A concentrations. Inadequate vitamin A supplementation after birth may exacerbate the problem, and contribute to an increased risk of developing chronic lung disease. A systematic review found that supplementing very low birth-weight infants with vitamin A was associated with a reduction in death or oxygen requirement at 1 month of age.[1]

1. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 12/03/08).

RESPIRATORY-TRACT INFECTIONS. Mortality studies did not show a consistent impact for vitamin A supplementation on death from non-measles-related respiratory infections.[1-3] Similarly, other studies have found no benefit of vitamin A on subsequent respiratory morbidity.[4-6] A meta-analysis of studies reporting pneumonia morbidity and mortality found no overall benefit or harm from vitamin A supplementation.[7] However, an increased prevalence of symptoms of respiratory infections associated with vitamin A supplementation has been noted in two studies,[8,9] particularly in children with adequate nutritional status. A meta-analysis of the effect of vitamin A supplementation on childhood morbidity found an increased incidence of respiratory-tract infections; since most trials had excluded children with overt vitamin A deficiency, the authors speculated that high-dose vitamin A given to children with adequate vitamin A stores might cause a temporary decline in immune status, increasing their susceptibility to infection.[10] A systematic review concluded that vitamin A should not be given to all children for *prevention* of acute lower respiratory-tract infections, but noted that children with vitamin A deficiency or poor nutritional status might benefit from supplementation in this respect.[11]

Vitamin A was not effective for the *treatment* of childhood non-measles-related lower respiratory-tract infections[12] or pneumonia.[13] Similarly, there was no benefit from vitamin A in the treatment of RSV infection in children in 2 studies.[14,15] In one of these studies there was a tendency for vitamin A to improve outcomes in the subgroup of severely ill children,[14] and in the other there was a slight increase in duration of hospitalisation in low-risk children receiving vitamin A.[15] A meta-analysis found no evidence that adjunctive treatment with high-dose vitamin A alters the course of pneumonia in children.[16]

1. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
2. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.
3. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.
4. Barreto ML, *et al.* Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 1994; **344:** 228–31.
5. Bhandari N, *et al.* Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *BMJ* 1994; **309:** 1404–7.
6. Kartasasmita CB, *et al.* Plasma retinol level, vitamin A supplementation and acute respiratory infections in children of 1-5 years old in a developing country. *Tubercle Lung Dis* 1995; **76:** 563–9.
7. The Vitamin A and Pneumonia Working Group. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. *Bull WHO* 1995; **73:** 609–19.
8. Stansfield SK, *et al.* Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; **342:** 578–82.
9. Dibley MJ, *et al.* Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; **126:** 434–42.
10. Grotto I, *et al.* Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003; **142:** 297–304.
11. Chen H, *et al.* Vitamin A for preventing acute lower respiratory tract infections in children up to seven years of age. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 12/03/08).
12. Kjolhede CL, *et al.* Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr* 1995; **126:** 807–12.
13. Nacul LC, *et al.* Randomised, double blind, placebo controlled clinical trial of efficacy of vitamin A treatment in non-measles childhood pneumonia. *BMJ* 1997; **315:** 505–10.
14. Dowell SF, *et al.* Treatment of respiratory syncytial virus infection with vitamin A: a randomised placebo-controlled trial in Santiago, Chile. *Pediatr Infect Dis J* 1996; **15:** 782–6.
15. Bresee JS, *et al.* Vitamin A therapy for children with respiratory syncytial virus infection: a multicenter trial in the United States. *Pediatr Infect Dis J* 1996; **15:** 777–82.
16. Brown N, Roberts C. Vitamin A for acute respiratory infection in developing countries: a meta-analysis. *Acta Paediatr* 2004; **93:** 1437–42.

XEROPHTHALMIA. Vitamin A deficiency is responsible in many developing countries for visual problems that may culminate in xerophthalmia and blindness.[1] Supplementation with vitamin A as recommended by WHO and discussed under Deficiency states, above, will raise the vitamin A status of the individual and act prophylactically against the development of xerophthalmia. For the treatment of xerophthalmia (which includes night blindness, conjunctival xerosis with Bitot's spots, corneal xerosis, corneal ulceration, and keratomalacia) WHO have stated[2] that oral doses of vitamin A, preferably in an oil-based preparation, are the treatment of choice and should be given immediately the disorder is recognised in the following doses:

- patients over 1 year of age (with the exception of women of reproductive age)—200 000 units
- infants aged 6 to 12 months—100 000 units
- those aged less than 6 months—50 000 units

Doses should be repeated the next day, and again at least 2 weeks later.

In *women of reproductive age* there is a need to balance the possible teratogenic effects of vitamin A should they be pregnant (see Pregnancy, above) with the serious consequences of xerophthalmia. WHO recommend that when there are severe signs of active xerophthalmia (i.e. acute corneal lesions) high-dose vitamin A treatment should be given as described above for those aged over 1 year. When only less severe signs are present (night blindness, Bitot's spots), women of reproductive age should receive a daily oral dose of 5000 to 10 000 units for at least 4 weeks. Alternatively, a weekly dose of not more than 25 000 units may be substituted.

Although xerophthalmia is far less common in developed countries, vitamin A deficiency should be considered in all patients with recurrent conjunctival or corneal disorders associated with gastrointestinal or liver disease.[3]

1. Smith J, Steinemann TL. Vitamin A deficiency and the eye. *Int Ophthalmol Clin* 2000; **40:** 83–91.
2. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*. 2nd ed. Geneva: WHO, 1997.
3. Watson NJ, *et al.* Vitamin A deficiency and xerophthalmia in the United Kingdom. *BMJ* 1995; **310:** 1050–1. Correction. *ibid.*: 1320.

Malignant neoplasms. Epidemiological studies suggest that antoxidant vitamins such as the vitamin A substances may play a role in preventing the development of malignancy but there is currently little evidence from prospective studies that supplementation is helpful, and even some evidence of harm (see p.1927). Conversely, synthetic retinoids such as tretinoin (all-*trans*-retinoic acid) have an established role in treating some cancers (see p.1619).

Retinitis pigmentosa. Retinitis pigmentosa is the name applied to a group of slowly progressive hereditary degenerative diseases of the retina[1] that often result in blindness in adulthood. The rod and cone photoreceptors in the retina are primarily affected and initial symptoms include night blindness and intolerance to light. Later signs include infiltration of pigment from the retinal pigmentary epithelium into the retinal layers. Various treatments have been tried but none appear to have any proven benefit. Results of one large double-blind study[2] suggest that whereas treatment with vitamin A might slow the decline in visual acuity treatment with vitamin E appears to have a deleterious effect on the rate of decline. Vitamin E did appear to delay the rate of vision decline in 3 patients with retinitis pigmentosa and a defect in α-tocopherol-transfer protein associated with vitamin E deficiency.[3] Supplementation with 15 000 units of vitamin A daily for up to 12 years was considered to be safe in a study in adults with retinitis pigmentosa; no clinical manifestations of hepatotoxicity were apparent.[4] Docosahexaenoic acid has also

been investigated, with variable results; some consider that vitamin A and oily fish in the diet could be beneficial in terms of visual preservation.[1] Transplantation of the retina is being investigated as a treatment for retinitis pigmentosa.[1,5] Devices to electrically stimulate the retina, optic nerve, or visual cortex are being developed.[1]

1. Hartong DT, *et al.* Retinitis pigmentosa. *Lancet* 2006; **368:** 1795–1809.
2. Berson EL, *et al.* A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol* 1993; **111:** 761–2.
3. Yokota T, *et al.* Retinitis pigmentosa and ataxia caused by a mutation in the gene for the α-tocopherol-transfer protein. *N Engl J Med* 1996; **335:** 1770–1.
4. Sibulesky L, *et al.* Safety of <7500 RE (<25 000 IU) vitamin A daily in adults with retinitis pigmentosa. *Am J Clin Nutr* 1999; **69:** 656–63.
5. Anonymous. Transplantation as a therapy for retinitis pigmentosa? *Br J Ophthalmol* 1997; **81:** 430.

Retinopathy of prematurity. There is some suggestion that vitamin A supplementation may reduce the incidence of retinopathy of prematurity (p.1994).

Preparations

BP 2008: Paediatric Vitamins A, C and D Oral Drops;
BPC 1973: Vitamins A and D Capsules;
USP 31: Oleovitamin A and D; Oleovitamin A and D Capsules; Vitamin A Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: A-Vitel; Adermicina A Mama; Amenite A†; Andrioderma; Arovit; Atomoderma A; Bagovit A; Cazmar; Domsedan; Fiosen-A†; Flavostat†; Masivol; Metabolite-A†; Midermus†; Rogadermis†; Skinderm A; ***Austral.:*** Ungvita; ***Austria:*** Arcavit A†; Avitol; Oleovit A; ***Belg.:*** Vitamuruine; ***Braz.:*** Arovit; Avitan†; Biocrin†; Lacrigel A; Retinar; ***Canad.:*** Arovit; ***Chile:*** Avitana; Bagovit A; Microret; ***Cz.:*** A-Mulsin†; Axerophthol; ***Denm.:*** A-vitamin; ***Fin.:*** A-Vitamiini†; ***Fr.:*** A 313; Arovit†; Avibon; ***Ger.:*** A-Mulsin†; A-Vicotrat†; Augenschutz NA; Oculotect; Oculotect sine; Solan-M; Vitadral; Vitafluid; Vitagel; ***Hung.:*** Oculotect; ***Israel:*** Avipur; ***Ital.:*** Arovit; Euvitol; Repervit†; Vit-A-N; ***Malaysia:*** Fairy ADE; ***Mex.:*** A Grin; A-Vicon†; Acon; Avinal-Ex†; Dermotin A; Microret; Microvita; Palmicaps†; Retigel-A; ***Neth.:*** Dagravit A Forte†; ***NZ:*** Dermalife; Ungvita; ***Philipp.:*** Afaxin; Alici-A; Hypotears; ***Pol.:*** Aksoderm; Dermosavit; Dermovit A; Masc Ochronna z Witamina A; Masc Witaminowa Ochronna; ***Port.:*** A-Vite; Vitaminoftalmina; ***Rus.:*** Vita-POS (Вита-ПОС); ***S.Afr.:*** Arovit; ***Spain:*** Auxina A Masiva; Biominol A; Dif Vitamin A Masivo†; Rinocusi Vitaminico; Rinovitex; ***Swed.:*** Arovit; ***Switz.:*** Arovit†; Oculotect; ***Turk.:*** Avicap; Avigen; Carovigen; ***UK:*** Biovit-A; ***USA:*** Aquasol A; Palmitate-A; Pedi-Vit-A; Retinol-A; ***Venez.:*** Alfa-Mon; Retiva.

Multi-ingredient: ***Arg.:*** A-D-C; A-Vitel E; AD Shock; Adermicina; Adermicina A; Atomoderma A-D; Atomoderma A-E; Aulo Gelio Pie; Baby-Tex; Bagovit A Plus; Bagovit Avant Piel; Calcusan Bebe; Celuvital†; Crema De Ordene; Derivoco†; Dermanova; Dermosan; Epitheliale A-Derma; Factor Vit AE; Glossderm†; Herbaccion Nutriderm†; Hipoglos; Hipoglos con Hidrocortisona; Masivol Urea; Medicreme; Nemegel†; O-Biol; Palan†; Panoxi; Platsul A; Puraloe Nutritivo; Redoxon A; Revital; Salvicutan†; Sulfadiazina de Plata; Sulfaplat; Ulcevarin†; Vagicural; Vansame; Vansame Plus; Vitapelen†; Zoodermina Cream; ***Austral.:*** Althaea Complex; Arthriforte; Bioglan Micelle A plus E; Bioglan Zn-A-C; Dermalife Plus; ER Cream†; Garlic, Horseradish, A & C Capsules†; Hydrastis Complex†; John Plunketts Protective Day Cream; Macro Natural Vitamin E Cream; Proyeast†; Sambucus Complex†; Trifolium Complex†; Verbascum Complex†; ***Austria:*** A-E-Mulsin; Arcavit A/E; Coldistop; Gelacet; Gerogelat; Lemuval; Oleovit; Oleovit A; Oleovit A + D; Regenerin†; Rovigon; Ultren; Vasovitol; ***Belg.:*** Neo-Cutigenol; Newderm†; Rovigon; Vita-Mefren†; ***Braz.:*** AD-Til; ADE 2 (Adedois); Adecal; Adederme; Adeforte; Aderogil D3; Babymed; Cariderm†; Dermalisan; Dermoden; Epitezan; Gaduol†; Glossaliv; Hipoderme; Hipodermon; Hipodex; Hipoglos; Licovit; Multiderme; Pronenen; Regencel; Regenom; Sensibaby; Solemil†; Suavederm; Vitadesan; ***Canad.:*** A & D; A & D Ointment†; Antiseptic Skin Cream†; Lubriderm Advanced Moisture†; Nutrol A D; ***Chile:*** Brexon†; Dermaglos; Dermaglos Plus†; Droxel; Microret K; Nenegloss; Panthoderm-A; Pediaderm†; Platsul A; Pomada Vitaminica; Povin; Rovigon; Sanoderm; ***Cz.:*** A-E-Mulsin†; Coldastop; Hypotears; Infadolan; ***Fin.:*** A-Vita; Aesol; Oftan A-Pant; Wicarba; Wicnevit; ***Fr.:*** Alpha 5 DS†; Cirkan a la Prednacinolone; Pommade Lelong†; Rovigon†; Seborheane; Solacy; ***Ger.:*** A + E Thilo†; A-E-Mulsin†; Coldastop; duraultra; Gelacet N†; Hewekzem novo N; Kwim†; Oculotect; Regepithel; Rememderm; Rovigon G†; Salus Augenschutz-Kapseln NA†; Tears Again; Unguentacid; Vita-POS; ***Gr.:*** Aquasol A+D; Aquasol A†; Avegon; Eviol-A; Novaquasol-A; ***Hong Kong:*** Aderma Epitheliale†; Hypotears†; Regepithel†; ***Hung.:*** Alksebor; Caldea†; Coldastop; Neogranormon; Vita-Merfen†; ***India:*** Medithane; Ossivite; Sclerobion; Sharkomalt; Sharkovit; ***Indon.:*** Oculotect; Scott's E Vita; Visivit; Vita-Vision; ***Israel:*** Aquitol†; Aronal Forte; Baby A + D; Neocutan Silver; Oleovit A + D †; Vita-Merfen NF; Vitamidyne A and D; ***Ital.:*** AD Pabyrn; Adisterolo; Babysteril; Derman-Oil; Dermana Crema; Dermana Pasta; Dicalcium†; Evitex; Granoleina†; Midium; Neoceuticals Spot Treatment; Provitamin A-E; Retinovit; Rinopanteina; Rovigon; Tocalfa; ***Mex.:*** Adekals; Adekon; Adekon C; Adeloren†; Adibal; Aquasol AD; Capent; Hipoglos; Hipoglos Cremoso; Kamiloderm; Microka; Microret K; Nutrem; Quinoret; Sutin†; Vidamil; Vitalorange; ***Neth.:*** Dagravit A-E Forte†; Halitran; ***Philipp.:*** Remederm; Rovigon; Vandol; ***Pol.:*** Alantavit; Capivit A + E; Oculotect; Tokovit A + E; Tranvit; ***Port.:*** Bacitracina Zimaia; Dermabut; Esclerobion; Rovigon; Synchrovit; ***S.Afr.:*** Vandol†; ***Spain:*** Adiod; Antihemorroidal†; Auxina A + E; Biominol A D; Calcio 20 Complex; Cicatral; Dermo Halibut; Epitelizante; Evitex A E Fuerte; Gramoce A; Grietalgen; Grietalgen Hidrocort†; Halibut; Halibut Hidrocortisona; Hubergrip†; Lacerdermol; Lacerdermol Complex; Mastiol; Mitosyl; Vicomin A C; Vitaber A E; Wobenzimal†; ***Swed.:*** AD-vitamin; ***Switz.:*** Alphastria; Antikeloides Creme; Carbamide Creme; Coldistop; Gelacet†; Lenideram†; Malvedrin; Oravil; Riccovitan†; Rovigon; Sanhelios Capsules a la vitamine A†; Unatol; Unguentolan; Vita-Hexin; Vita-Merfen; ***Turk.:*** Balya; ***UK:*** S.P.H.P. Se-Power; ***USA:*** A and D Medicated; Aloe Grande; Clocream; Diaper Guard; Lazercreme; Lobana Derm-Aide; Lobana Peri-Garde; Paladin; Phicon; ***Venez.:*** A-D-Vit; Adaderm; Ademina; Adenar; Dicalcico†; Hipoglos†; Vandol; Vitenol†.

Vitamin B Substances

Vitamina B, grupo de la.

The B vitamin group includes the B_1 substances (thiamine and its derivatives), B_2 (riboflavin), B_6 (pyridoxine and derivatives), and B_{12} (the cobalamins). In addition, nicotinic acid and its derivatives (p.1957) and folic acid (p.1940) are held to be part of the group, as is pantothenic acid (p.1959), but these latter substances are not generally referred to by their traditional B nomenclature.

Preparations

Proprietary Preparations (details are given in Part 3)

Philipp.: Vaneular.

Multi-ingredient: ***Braz.:*** Plex B; Xantina B12†; Xantinon B12; ***India:*** Elferri†; Hycibex; JP Tone; Livogen†; Lupizyme; Terramycin SF; Toniazol†; Vitexid; ***Indon.:*** Gunabion; Lesifit; Tonikum; ***Malaysia:*** Hepavite; Time Release Nutrition Mega B + C Complex†; ***Philipp.:*** IBC; ***Singapore:*** Hepavite.

Used as an adjunct in: ***Philipp.:*** Trisofort.

Vitamin B_1 Substances

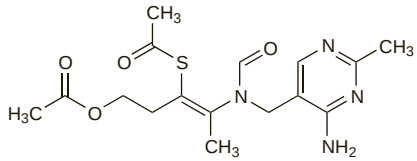
Vitamina B_1.

Acetiamine Hydrochloride *(rINNM)*

Acethiamine Hydrochloride; Acétiamine, Chlorhydrate d'; Acetiamini Hydrochloridum; Diacethiamine Hydrochloride; Hidrocloruro de acetiamina. *N*-(5-Acetoxy-3-acetylthiopent-2-en-2-yl)-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide hydrochloride monohydrate.

Ацетиамина Гидрохлорид

$C_{16}H_{22}N_4O_4S,HCl,H_2O$ = 420.9.
CAS — 299-89-8 (acetiamine).



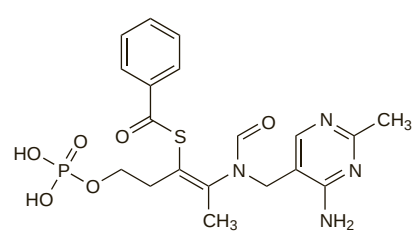
(acetiamine)

Benfotiamine *(rINN)*

Benfotiamina; Benfotiaminum; *S*-Benzoylthiamine *O*-Monophosphate. *N*-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-(2-benzoylthio-4-dihydroxyphosphinyloxy-1-methylbut-1-enyl)formamide.

Бенфотиамин

$C_{19}H_{23}N_4O_6PS$ = 466.4.
CAS — 22457-89-2.
ATC — A11DA03.
ATC Vet — QA11DA03.

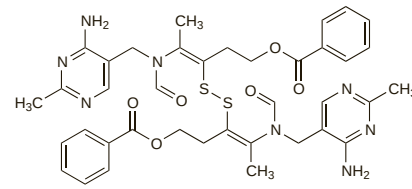


Bisbentiamine *(rINN)*

O-Benzoylthiamine Disulphide; Bisbentiamina; Bisbentiaminum. *NN'*-{Dithiobis[2-(2-benzoyloxyethyl)-1-methylvinylene]}bis[*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide].

Бисбентиамин

$C_{38}H_{42}N_8O_6S_2$ = 770.9.
CAS — 2667-89-2.

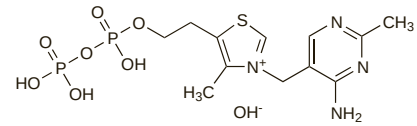


Cocarboxylase *(BAN, rINN)*

Cocarboxilasa; Co-carboxylase; Cocarboxylasum; Diphosphothiamine; Pyruvodehydrase; Thiamine Pyrophosphate. 3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-{2-[dihydroxyphosphinyloxy-(hydroxy)phosphinyloxy]ethyl}-4-methylthiazolium hydroxide.

Кокарбоксилаза

$C_{12}H_{20}N_4O_8P_2S$ (hydroxide form) = 442.3.
CAS — 154-87-0 (cocarboxylase chloride).



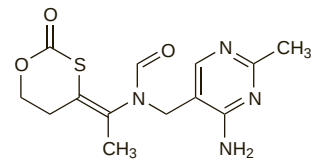
Pharmacopoeias. *Pol.* includes the chloride.

Cycotiamine *(rINN)*

CCT; Cicotiamina; Cyclocarbothiamine; Cycotiaminum. *N*-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-[1-(2-oxo-1,3-oxathian-4-ylidene)ethyl]formamide.

Цикотиамин

$C_{13}H_{16}N_4O_3S$ = 308.4.
CAS — 6092-18-8.

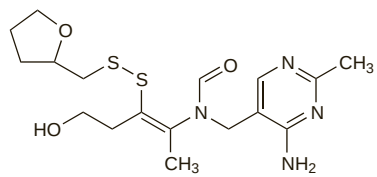


Fursultiamine *(rINN)*

Fursultiamina; Fursultiaminum; Thiamine Tetrahydrofurfuryl Disulphide; TTFD. *N*-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-[4-hydroxy-1-methyl-2-(tetrahydrofurfuryldithio)but-1-enyl]formamide.

Фурсультиамин

$C_{17}H_{26}N_4O_3S_2$ = 398.5.
CAS — 804-30-8.



Octotiamine *(rINN)*

Octotiamina; Octotiaminum; Oktotiamiini; Oktotiamin; TATD; Thioctothiamine. *N*-[2-(3-Acetylthio-7-methoxycarbonylheptyldithio)-4-hydroxy-1-methylbut-1-enyl]-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide.

Октотиамин

$C_{23}H_{36}N_4O_5S_3$ = 544.8.
CAS — 137-86-0.