5. Yoshizawa K, *et al.* Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998; **90:** 1219–24.
6. Li H, *et al.* A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst* 2004; **96:** 696–703.
7. Brinkman M, *et al.* Use of selenium in chemoprevention of bladder cancer. *Lancet Oncol* 2006; **7:** 766–74.

Preparations

USP 31: Selenious Acid Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Selebound; ***Austria:*** Selen; Selenase; ***Cz.:*** Selenase; ***Fr.:*** Plexium; Selenion; ***Ger.:*** Cefasel; Seleject; Selemun†; Selen-loges; Selenase; Seltrans; ***Hong Kong:*** Selepen; ***Mex.:*** Selefusin†; ***Neth.:*** Selenase; ***Pol.:*** Cerosel; ***Port.:*** Selenase; ***Switz.:*** Selenase; ***Turk.:*** Selenase; ***UK:*** Selenase; ***USA:*** Sele-Pak; Selepen.

Multi-ingredient: ***Arg.:*** Centella Asiatica Compuesta; ***Canad.:*** Selenium Plus; ***Chile:*** Natursel-C; ***Fr.:*** Bio-Selenium; Phytosolaire; Selenium-ACE; ***Indon.:*** Ekinase; Imulan; Stacare; ***Irl.:*** Antox; ***Ital.:*** Fosfarsile Forte; Influ-Zinc; Longevital; Neomyrt Plus; Selenium-ACE; Tannidin Plus; ***Port.:*** Rilastil Dermo Solar; Selenium-ACE†; ***Thai.:*** Bio-Selenium Zinc; ***UK:*** Se-Power; Selene-Activ; ***Venez.:*** Kalsis.

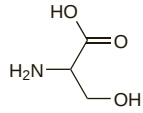
Serine *(USAN, rINN)*

β-Hydroxyalanine; S; Ser; Seriini; Serin; Serina; Serinas; Sérine; L-Serine; Serinum; Seryna; Szerin. L-2-Amino-3-hydroxypropionic acid.

Серин

$C_3H_7NO_3$ = 105.1.

CAS — 56-45-1 (serine); 302-84-1 (DL-serine).



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Serine). White or almost white crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. Protect from light.
USP 31 (Serine). White, odourless crystals. Soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Serine is a non-essential amino acid. It is used as a dietary supplement.

The racemic form (DL-serine) has been included in iron supplements to increase iron absorption.

Preparations

Proprietary Preparations (details are given in Part 3)

Used as an adjunct in: ***Austria:*** Aktiferrin; Aktiferrin Compositum; ***Cz.:*** Aktiferrin; Aktiferrin Compositum; ***Hung.:*** Aktiferrin; ***Israel:*** Aktiferrin-F; ***Malaysia:*** Aktiferrin-F; ***Rus.:*** Aktiferrin (Актиферрин); Aktiferrin Compositum (Актиферрин Композитум); ***Singapore:*** Aktiferrin-F; ***Switz.:*** Actiferrine; Actiferrine-F Nouvelle formule.

Sodium Feredetate *(BAN, rINN)*

Ferédétate de Sodium; Feredetato sódico; Natrii Feredetas; Sodium Ironedetate. The monohydrated iron chelate of the monosodium salt of ethylenediamine-*NNN′N′*-tetra-acetic acid; Iron (III) sodium ethylenediaminetetra-acetate monohydrate.

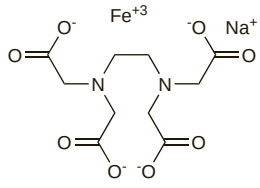
Натрия Фередетат

$C_{10}H_{12}FeN_2NaO_8.H_2O$ = 385.1.

CAS — 15708-41-5 (anhydrous sodium feredetate).

ATC — B03AB03.

ATC Vet — QB03AB03.



(anhydrous sodium feredetate)

Pharmacopoeias. In *Br.*
BP 2008 (Sodium Feredetate). A yellow or yellowish brown, hygroscopic, crystalline powder. A 1% solution in water has a pH of 4.0 to 6.5. Store in airtight containers.

Profile

Sodium feredetate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 1.42 g daily (equivalent to up to about 205 mg of iron daily).

Preparations

BP 2008: Sodium Feredetate Oral Solution.

Proprietary Preparations (details are given in Part 3)
Fr.: Ferrostrane; ***Philipp.:*** Ferrosmate; ***UK:*** Sytron.

Sodium Ferric Gluconate Complex *(USAN)*

Ferric Sodium Gluconate; D-Gluconic acid, iron (3+) sodium salt; Hierro gluconato sódico, complejo de; Iron Gluconate; Natrii ferrigluconas; Sodium Ferric Gluconate; Sodium ferrigluconate; Sodium-Iron(III) Gluconate Complex.

$[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5]_x$.

CAS — 34089-81-1.

ATC Vet — QB03AC07.

NOTE. Distinguish from Ferrous Gluconate.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p.1951.

Hypersensitivity. For a discussion as to whether sodium ferric gluconate complex may be a safer alternative to iron dextran, see p.1952.

Pharmacokinetics

Peak concentrations vary with the dose and rate at which sodium ferric gluconate complex is given. The volume of distribution does not appear to vary according to dose or rate. Elimination half-life varies by dose, and has been reported to be 0.85 hours for a dose of 62.5 mg and 1.45 hours for a dose of 125 mg; doses were given by slow intravenous injection.

Uses and Administration

Sodium ferric gluconate complex is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given as a solution containing the equivalent of 12.5 mg/mL of elemental iron. The recommended dose for haemodialysis patients who are receiving epoetin therapy is 125 mg iron (10 mL) diluted in 100 mL sodium chloride 0.9%, and given as an intravenous infusion over 1 hour; it may also be given undiluted as a slow intravenous injection (at a rate of 12.5 mg/minute) during dialysis. This dose is usually repeated over 8 dialysis sessions to achieve a favourable response. Children 6 years of age and older may be given 1.5 mg/kg of elemental iron (0.12 mL/kg), diluted in 25 mL sodium chloride 0.9% and infused over 1 hour, up to a maximum of 125 mg per dose.

Anaemia of chronic renal failure. References.

1. Yorgin PD, *et al.* Sodium ferric gluconate therapy in renal transplant and renal failure patients. *Pediatr Nephrol* 2000; **15:** 171–5.
2. Fishbane S, Wagner J. Sodium ferric gluconate complex in the treatment of iron deficiency for patients on dialysis. *Am J Kidney Dis* 2001; **37:** 879–83.
3. Folkert VW, *et al.* Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher dose (> or =250 mg) administration. *Am J Kidney Dis* 2003; **41:** 651–7.
4. Michael B, *et al.* Sodium ferric gluconate complex in haemodialysis patients: a prospective evaluation of long-term safety. *Nephrol Dial Transplant* 2004; **19:** 1576–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Pentaferr; ***Cz.:*** Ferrlecit; ***Ger.:*** Ferrlecit; ***Hung.:*** Ferrlecit; ***India:*** Efecient; ***Israel:*** Ferrlecit; ***Ital.:*** Actiferro†; Epaplex 40†; Extrafer; Ferlixit; Ferri-Emina†; Ferritin Oti; Ferrosprint; Fevital Simplex†; Hemocromo; Inferil†; Rossepar; Rubroferrina†; Sanifer; ***USA:*** Ferrlecit.

Multi-ingredient: ***Ital.:*** Ferritin Complex; ***Port.:*** Ferritin Oti.

Sodium Fluoride

Fluorid sodný; Fluoruro sódico; Natrii fluoridum; Natrio fluoridas; Natrium Fluoratum; Natriumfluorid; Nátrium-fluorid; Natriumfluoridi; Sodium, fluorure de; Sodu fluorek; Sodyum Fluorür.

NaF = 41.99.

CAS — 7681-49-4.

ATC — A01AA01; A12CD01.

ATC Vet — QA01AA01; QA12CD01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Sodium Fluoride). A white or almost white powder or colourless crystals. Soluble in water; practically insoluble in alcohol.
USP 31 (Sodium Fluoride). A white, odourless powder. Soluble 1 in 25 of water; insoluble in alcohol.

Adverse Effects and Treatment

In the controlled amounts recommended for fluoridation of drinking water and at the recommended doses used in dentistry for caries prophylaxis, sodium fluoride has not been shown to have significant adverse effects.

In **acute** poisoning, sodium fluoride taken by mouth is corrosive, forming hydrofluoric acid in the stomach. Adverse effects include a salty or soapy taste, increased salivation, gastrointestinal disturbances, abdominal pain, weakness, drowsiness, faintness, and shallow breathing; more serious effects include hypocalcaemia, hypomagnesaemia, hyperkalaemia, tremors, hyperreflexia, tetany, convulsions, cardiac arrhythmias, shock, respiratory arrest, and cardiac failure. Death may occur within 2 to 4 hours. Although there is much interindividual variation, a single oral dose of 5 to 10 g of sodium fluoride would be considered lethal in an untreated adult by most authorities. However, severe poisoning has been reported after oral doses of less than 1 g, and the minimum dose that can cause possibly fatal toxicity in children has been suggested to be 5 mg/kg of fluoride ion.

Treatment of acute poisoning involves gastric lavage with lime water or a weak solution of another calcium salt to precipitate fluoride, maintenance of high urine output, slow intravenous injections of calcium gluconate 10% for hypocalcaemia and tetany, and symptomatic and supportive measures. Magnesium sulfate may be given to correct hypomagnesaemia, and aluminium hydroxide may also reduce fluoride absorption. Haemodialysis may be considered.

Chronic fluoride poisoning may result in skeletal fluorosis, manifestations of which include increased density and coarsened trabeculation of bone and calcification in ligaments, tendons, and muscle insertions. Clinical signs are bone pain, stiffness, limited movement, and in severe cases, crippling deformities. Prolonged excessive intake by children during the period of tooth development before eruption can result in dental fluorosis characterised by mottled enamel. At fluoride concentrations in drinking water of 1 to 2 ppm (1 to 2 mg/litre) dental fluorosis is mild with white opaque flecks on the teeth. At higher concentrations, enamel defects become more severe with brown to black staining and the teeth have a pitted corroded appearance.

The **fluoridation** of water (below) has been a subject of considerable controversy. Suggestions that it increases the incidence of thyroid disorders, chromosome aberrations, and cancer have not been substantiated.

◊ Reviews of the toxic effects of fluoride salts.

1. WHO. Fluorine and Fluorides. *Environmental Health Criteria 36*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc36.htm (accessed 08/11/05)
2. Whitford GM. The physiological and toxicological characteristics of fluoride. *J Dent Res* 1990; **69** (Spec Iss): 539–49.
3. Whitford GM. The metabolism and toxicity of fluoride. *Monogr Oral Sci* 1996; **16:** 1–153.
4. WHO. Fluorides. *Environmental Health Criteria 227*. Geneva: WHO, 2002. Available at: http://www.inchem.org/documents/ehc/ehc/ehc227.htm (accessed 08/11/05)

Carcinogenicity. Based on comparisons of cancer mortality rates for communities residing in fluoridated and non-fluoridated cities, it was alleged that artificial fluoridation of water might be associated with an increased risk of cancer.[1] Re-examination of these data by others did not confirm the relationship, nor did further studies in a number of countries.[2] In Great Britain, the Working Party on Fluoridation of Water and Cancer[3] found nothing that could lead them to conclude that either fluoride occurring naturally in water, or fluoride added to water supplies, was capable of inducing cancer, or of increasing the mortality from cancer. In this respect, fluoridation of drinking water was considered safe. Further study in *animal* models by the USA National Toxicology Programme[4] found no evidence of carcinogenicity in female *rats* or in *mice* of either sex. A small number of osteosarcomas was found in male *rats* in the medium- and high-dose groups, although the association between sodium fluoride and the tumour was uncertain. A review of epidemiological evidence of possible carcinogens in drinking water stated that additional data gathered since 1990 did not support an association between the risk of osteosarcoma, or any other cancer, and the fluoride in drinking water.[5]

A cohort study of workers exposed to high levels of fluoride dust reported excess incidences of primary lung cancer and bladder tumours.[6]

1. Yiamouyiannis J, Burk D. Fluoridation and cancer: age-dependence of cancer mortality related to artificial fluoridation. *Fluoride* 1977; **10**: 102–25S.
2. Clemmesen J. The alleged association between artificial fluoridation of water supplies and cancer: a review. *Bull WHO* 1983; **61:** 871–83.

3. DHSS. *Fluoridation of water and cancer: a review of the epidemiological evidence: report of the working party.* London: HMSO, 1985.
4. Public Health Service report on fluoride benefits and risks. *JAMA* 1991; **266:** 1061–2, 1066–7.
5. Cantor KP. Drinking water and cancer. *Cancer Causes Control* 1997; **8:** 292–308.
6. Grandjean P, Olsen JH. Extended follow-up of cancer incidence in fluoride-exposed workers. *J Natl Cancer Inst* 2004; **96:** 802–3.

Effects on bones and joints. Exacerbation of **rheumatoid arthritis** in a 68-year-old woman was attributed to sodium fluoride given in a dose equivalent to 22 mg of fluorine daily for osteoporosis.[1]

An increased risk of **hip fracture** in the elderly has been suggested as being associated with fluoridated water;[2] another study[3] reported that this association was confined to fluoride concentrations of more than 110 micrograms/litre. However, a large case-control study[4] found no increase in the risk of hip fracture for people ingesting fluoridated water at concentrations of about 1 mg/litre (1 ppm). Similarly, a large prospective study[5] in older white women found no increase in the risk of fractures with long-term exposure to fluoridated drinking water, and even a suggestion of a reduction in the risk of fractures of the hip and vertebrae, due to increased bone mineral density of the femoral neck and lumbar spine, in those women continuously exposed to fluoridation. An epidemiological study in a large rural Chinese population determined that long-term fluoride exposure from drinking water containing 4.32 ppm or more increased the risk of overall fracture as well as hip fracture. Water containing 1 to 1.06 ppm decreased the risk of overall fractures relative to areas with negligible water fluoridation; a similar protective effect on the risk of hip fractures was not seen. Although the number of hip fractures were small, the authors suggested that this supported other findings that fluoride concentrations of about 1 ppm in drinking water do not increase the risk of hip fracture.[6] For comment on the influence of therapeutic doses of fluoride on the incidence of fractures, see below under Osteoporosis in Uses and Administration.

Use of fluoride, particularly in doses of 40 mg or more daily, may be associated with a **peripheral pain syndrome**, usually manifested as bone pain in the distal lower limbs, but sometimes involving the upper limbs and axial skeleton. The cause is uncertain: both stress fractures and increased bone growth at the site of pain have been proposed.[7]

Fluoride-related **bone disease** (skeletal fluorosis) manifesting as osteomalacia or osteosclerosis, has been reported after excessive consumption of tea (brewed, bottled, or iced).[8,9] Some bottled teas were found to have fluoride concentrations above the FDA's limit of 2.4 ppm for bottled beverages.[9]

1. Duell PB, Chesnut CH. Exacerbation of rheumatoid arthritis by sodium fluoride treatment of osteoporosis. *Arch Intern Med* 1991; **151:** 783–4.
2. Danielson C, *et al.* Hip fractures and fluoridation in Utah's elderly population. *JAMA* 1992; **268**: 746–8.
3. Jacqmin-Gadda H, *et al.* Fluorine concentration in drinking water and fractures in the elderly. *JAMA* 1995; **273:** 775–6.
4. Hillier S, *et al.* Fluoride in drinking water and risk of hip fracture in the UK: a case-control study. *Lancet* 2000; **355:** 265–9.
5. Phipps KR, *et al.* Community water fluoridation, bone mineral density, and fractures: prospective study of effects in older women. *BMJ* 2000; **321:** 860–4.
6. Li Y, *et al.* Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. *J Bone Miner Res* 2001; **16:** 932–9.
7. Jones G, Sambrook PN. Drug-induced disorders of bone metabolism: incidence, management and avoidance. *Drug Safety* 1994; **10:** 480–9.
8. Hallanger Johnson JE, *et al.* Fluoride-related bone disease associated with habitual tea consumption. *Mayo Clin Proc* 2007; **82:** 719–24. Correction. *ibid.*; 1017. [dosage error]
9. Whyte MP. Fluoride levels in bottled teas. *Am J Med* 2006; **119:** 189–90.

Effects on the kidneys. Nephrotoxicity has been associated with high plasma concentrations of fluoride during anaesthesia with fluorine-containing anaesthetics such as methoxyflurane (p.1789). Elevated fluoride ion concentrations have also been noted in the plasma of patients receiving enflurane or isoflurane, although no clinical effect on renal function was found (see Effects on the Kidneys, p.1782 and Metabolism, p.1786).

Fluorosis. Discussions of chronic fluorosis.[1-5] In a 1994 report, WHO considered that in temperate climates, *teeth* seemed not to be affected if fluoride concentrations in drinking water were not greatly above 1 ppm; fluorosis affecting bone had not been detected at concentrations of 4 to 8 ppm in temperate regions, although it could occur at concentrations of more than 6 ppm in tropical areas.[6] However, a later systematic review[7] of the effects of water fluoridation, which included 214 studies worldwide, considered that at a concentration of 1 ppm, an estimated 12.5% of exposed people would develop sufficient fluorosis of their teeth to cause aesthetic concern. Swallowing of fluoridated toothpaste by young children has been implicated as a risk factor for fluorosis.[4,8] Higher concentrations of fluoride in toothpaste have been associated with less caries, but with higher levels of fluorosis,[9] and toothpastes with lower concentrations of fluoride have been recommended for use in children.[8,9] The use of infant formula feeds reconstituted with fluoridated water may result in ingestion of large amounts of fluoride[5] and subsequent fluorosis;[3] bottled water may also contain fluoride.[5]

Skeletal fluorosis associated with excess tea consumption has also been reported (see Effects on Bones and Joints, above).

1. Anonymous. Chronic fluorosis. *BMJ* 1981; **282:** 253–4.
2. Mason JO. A message to health professionals about fluorosis. *JAMA* 1991; **265**: 2939.
3. Horowitz HS. Proper use of fluoride products in fluoridated communities. *Lancet* 1999; **353:** 1462.
4. Whelton HP, *et al.* A review of fluorosis in the European Union: prevalence, risk factors and aesthetic issues. *Community Dent Oral Epidemiol* 2004; **32** (suppl): 9–18.
5. Levy SM. An update on fluorides and fluorosis. *J Can Dent Assoc* 2003; **69:** 286–91.
6. WHO. Fluorides and oral health: report of a WHO expert committee on oral health status and fluoride use. *WHO Tech Rep Ser 846* 1994.
7. McDonagh MS, *et al.* Systematic review of water fluoridation. *BMJ* 2000; **321:** 855–9.
8. Rock WP, Sabieha AM. The relationship between reported toothpaste usage in infancy and fluorosis of permanent incisors. *Br Dent J* 1997; **183:** 165–70.
9. Steiner M, *et al.* Effect of 1000 ppm relative to 250 ppm fluoride toothpaste: a meta-analysis. *Am J Dent* 2004; **17:** 85–8.

Gum disease. In the Davangere district of India, the fluoride concentration in the drinking water ranges from 1.5 to 3 ppm; there is virtually no dental care. In a study of patients with dental fluorosis in this district, a strong association was found between the occurrence of periodontal disease and the severity of fluorosis; periodontitis was also high in subjects with poor oral hygiene. Gingivitis reduced as the degree of fluorosis increased. Fluoride may have a role in the etiology and pathogenesis of gum disease.[1]

1. Vandana KL, Reddy MS. Assessment of periodontal status in dental fluorosis subjects using community periodontal index of treatment needs. *Indian J Dent Res* 2007; **18:** 67–71.

Hypersensitivity. Dermatitis, urticaria, headaches, gastrointestinal reactions, stomatitis, and mouth ulcers have all been reported as hypersensitivity reactions after use of fluoride-containing toothpastes, tablets, drops or drinking water.[1] Topical treatment of the teeth with a sodium fluoride preparation has been reported to cause severe disseminated acute urticaria and facial angioedema, requiring hospitalisation.[2] However, 2 other cases of reaction to the same commercial preparation were considered to be due to colophony (p.2286) contained in the preparation.[3] It has been suggested that, in cases of probable toothpaste allergy, lack of response to patch tests on the skin may be because fluoride crosses the oral mucous membrane more easily than the skin.[4]

Stomatitis has also been reported after use of gels containing olaflur and dectaflur.[5]

1. Mummery RV. Claimed fluoride allergy. *Br Dent J* 1984; **157:** 48.
2. Camarasa JG, *et al.* Contact urticaria from sodium fluoride. *Contact Dermatitis* 1993; **28:** 294.
3. Isaksson M, *et al.* Contact allergy to Duraphat. *Scand J Dent Res* 1993; **101:** 49–51.
4. Brun R. Recurrent benign aphthous stomatitis and fluoride allergy. *Dermatology* 2004; **208:** 181.
5. Ganter G, *et al.* Contact dermatitis and stomatitis due to amine fluoride. *Contact Dermatitis* 1997; **37:** 248.

Overdosage. References.

1. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5:** 79–85.
2. Gessner BD, *et al.* Acute fluoride poisoning from a public water system. *N Engl J Med* 1994; **330:** 95–9.
3. Arnow PM, *et al.* An outbreak of fatal fluoride intoxication in a long-term hemodialysis unit. *Ann Intern Med* 1994; **121:** 339–44.
4. Shulman JD, Wells LM. Acute fluoride toxicity from ingesting home-use dental products in children, birth to 6 years of age. *J Public Health Dent* 1997; **57:** 150–8.

Precautions

When considering fluoride supplementation, allowance should be made for fluorides ingested from other sources; fluoride supplements in children are not generally recommended when the fluoride content of drinking water is over 0.7 ppm (0.6 ppm in the USA) (see also Uses and Administration, below). Care should be taken to prevent children swallowing excessive fluoride after topical application to teeth.

Patients with impaired renal function may be particularly susceptible to fluorosis. Regular dialysis with fluoridated water may result in additional fluoride absorption; a maximum concentration of 0.2 ppm of fluoride in the dialysate has been recommended. Dialysis patients not using deionised water are at risk from changes in the fluoride content of the water supply.

Interactions

Aluminium, calcium, and magnesium salts may decrease the absorption of fluoride.

Pharmacokinetics

Sodium fluoride and other soluble fluorides are readily absorbed from the gastrointestinal tract. Inhaled fluorides (from industrial fumes and dusts) are absorbed through the lungs. Fluoride is deposited mainly in the bones and teeth. It is principally excreted in the urine but small amounts may also be excreted in faeces and sweat. It crosses the placenta and is present in saliva, nails, and hair. There is some evidence of distribution into breast milk.

Uses and Administration

Sodium fluoride is used to prevent dental caries and may be used to increase bone density in osteoporosis (see below). Sodium fluoride is used as a source of fluoride in total parenteral nutrition.

The content of sodium fluoride is usually expressed in terms of the fluoride; 2.2 mg of sodium fluoride is equivalent to about 1 mg of fluoride. Each g provides about 23.8 mmol of sodium and fluoride.

For **dental caries prophylaxis**, sodium fluoride is used as an adjunct to diet and oral hygiene. It may render the enamel of teeth more resistant to acid, promote remineralisation, or reduce microbial acid production. Fluoride can be given by *fluoridation* of the public water supply (below) to achieve a usual fluoride concentration of 1 ppm in temperate regions. The concentration may vary from 0.6 to 1.2 ppm depending on the climatic temperature with the lower concentrations being used in hotter regions where more water is likely to be consumed. Fluoridation of salt at a minimum concentration of 200 mg of fluoride per kg of salt is an alternative. Fluoridation of milk has been tried in some countries.

Alternatively, sodium fluoride may be given as an *oral supplement* to children considered to be at high risk of caries. The daily dosage should be adjusted for the fluoride content of the drinking water, for fluorides ingested from other sources such as the diet, and for the age of the child. Guidelines in the USA and the UK both suggest that, where the drinking water contains less than 0.3 ppm of fluoride, children may be given the following doses according to age:

- under 6 months, not recommended
- 6 months to 3 years, sodium fluoride 0.55 mg (equivalent to 0.25 mg of fluoride) daily
- 3 to 6 years, 1.1 mg (equivalent to 0.5 mg of fluoride) daily
- 6 years and over, 2.2 mg (equivalent to 1 mg of fluoride) daily.

When drinking water contains 0.3 to 0.7 ppm (0.3 to 0.6 ppm in the USA) of fluoride lower doses should be considered. Specifically, it is recommended that no additional fluoride should be given to children less than 3 years of age and for older children the above doses should be halved. If the water contains more than 0.7 ppm (0.6 ppm in the USA) of fluoride, supplementation is not recommended. Tablets should be sucked or chewed before swallowing since the topical action of fluoride on enamel and plaque is considered to be more important than the systemic effect. The value of giving fluoride during pregnancy, to benefit the child, is not established. Dental benefits from the use of dietary fluoride supplements by adults are unsubstantiated.

After tooth eruption, *local application* of fluoride is effective. Daily mouth-rinses of sodium fluoride 0.05% (about 225 ppm fluoride) or weekly mouth-rinses of sodium fluoride 0.2% (900 ppm) may be used, but are not recommended for children aged under 6 years because they are unable to effectively spit the rinse out after use. Sodium fluoride 2% (about 9090 ppm) solution is available for topical use, under professional supervision. Fluoridated toothpastes are now widely available and are a convenient source of fluoride. In the UK, the maximum permitted fluoride level in conventional toothpastes is sodium fluoride 0.32% (0.15% or 1500 ppm fluoride); higher concentrations of sodium fluoride 0.619% (2800 ppm fluoride) are available un-

der professional supervision. Formulations for children under 7 years of age typically contain sodium fluoride 0.11% (500 ppm); higher concentrations may be used, but the amount applied should be supervised to avoid excessive use or ingestion. Sodium fluoride has also been applied topically as a varnish under professional supervision. Alternatively, sodium fluoride solutions or gels acidified with phosphoric acid (commonly known as acidulated phosphate fluoride preparations) may be used. These preparations are considered to increase the fluoride uptake by the enamel and protect the enamel from demineralisation. For maximum benefit, eating, drinking, or rinsing should be avoided for at least 15 to 30 minutes after topical fluoride application.

Other fluoride compounds used in oral hygiene products and toothpastes include aluminium fluoride, ammonium fluoride, calcium fluoride (p.1932), dectaflur (p.1937), magnesium fluoride (p.1955) nicomethanol hydrofluoride, olaflur (p.1959), potassium fluoride, sodium monofluorophosphate (p.1964), and stannous fluoride (p.1967). Other fluorides used in the fluoridation of water supplies include sodium silicofluoride (p.1965).

Sodium fluoride has also been used, like some other fluoride compounds, in **rodenticides** and **insecticides**.

Dental caries prophylaxis. There is strong and consistent evidence in favour of the effectiveness of fluoride in preventing or reducing the incidence of dental caries. However, there is no strong evidence that one form of topical fluoride is more effective than another.

References.

1. WHO. Fluorides and oral health: report of a WHO expert committee on oral health status and fluoride use. *WHO Tech Rep Ser 846* 1994.
2. Anonymous. Fluoride supplement dosage: a statement by the British Dental Association, the British Society of Paediatric Dentistry and the British Association for the Study of Community Dentistry. *Br Dent J* 1997; **182:** 6–7.
3. Craig GC. Fluorides and the prevention of dental decay: a statement from the Representative Board of the British Dental Association. *Br Dent J* 2000; **188:** 654.
4. CDC. Recommendations for using fluoride to prevent and control dental caries in the United States. *MMWR* 2001; **50** (RR-14): 1–42. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5014.pdf (accessed 08/11/05)
5. Marinho VCC, *et al.* Fluoride gels for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 08/11/05).
6. Marinho VCC, *et al.* Fluoride varnishes for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 08/11/05).
7. Marinho VCC, *et al.* Fluoride toothpastes for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 08/11/05).
8. Marinho VCC, *et al.* Fluoride mouthrinses for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 08/11/05).
9. Twetman S, *et al.* Caries-preventive effect of fluoride toothpaste: a systematic review. *Acta Odontol Scand* 2003; **61:** 347–55.
10. Marinho VCC, *et al.* One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 08/11/05).
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16. WHO/FDI World Dental Federation/International Association for Dental Research. Beijing declaration: call to action to promote oral health by using fluoride in China and Southeast Asia (issued September 2007). Available at: http://www.fdiworldental.org/public_health/assets/Fluoride_Consultation/Beijing_Declaration_English.pdf (accessed 10/03/08)

Fluoridation of water. Some countries add fluoride to water supplies to prevent dental caries. This has been the subject of much controversy.

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Human requirements. In the USA dietary reference intakes have been set for fluoride. These propose an adequate intake (see p.1925) for dental caries prevention to be 4 mg daily in adult men and 3 mg in women;[1] lower values are suggested in children and adolescents, depending on age. The tolerable upper intake level is 10 mg daily in adults.[1]

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Osteoporosis. Fluoride has been used in the treatment of osteoporosis (p.1084) to improve bone strength by inducing subclinical fluorosis. The main effect of fluoride on the skeleton is to stimulate osteoblasts and increase trabecular bone mass. Because antiresorptive drugs cannot restore lost bone mass, this is potentially valuable in the treatment of osteoporosis. However, too much fluoride can increase bone fragility, and the overall effect of sodium fluoride on the incidence of fracture has not been established.

A controlled study in patients with postmenopausal osteoporosis[1] found that sodium fluoride 75 mg daily with a calcium supplement increased trabecular bone mass of the spine but did not reduce the incidence of vertebral fractures. Patients given sodium fluoride also had a higher incidence of nonvertebral fractures. An extension and re-analysis of the study,[2] however, showed that gradual increases in bone mass observed in patients taking lower doses of sodium fluoride (down to about 40 mg daily) were associated with a decrease in the incidence of fractures. A previous study[3] had reported a beneficial effect in vertebral fracture rate in patients with primary osteoporosis and at least one vertebral crush fracture. In this study sodium fluoride was given in a daily dose of 50 mg; calcium and vitamin D were also given. Interim analysis of a subsequent study using a slow-release formulation of sodium fluoride 50 mg daily taken intermittently with a regular calcium supplement showed a decrease in vertebral fractures of 50% at 2.5 years.[4] At 4 years the beneficial effect was sustained, the main effect being seen in a reduced incidence of new vertebral fractures;[5] no reduction was seen in the incidence of recurrent fractures but this study found no evidence of an increase in nonvertebral fractures. Some consider that low-dose fluoride can be of benefit in established postmenopausal osteoporosis, but the therapeutic window is narrow, and calcium and vitamin D must also be given to meet the calcium demand and avoid resorption of established bone.[6] A further double-blind study failed to show a reduction in vertebral fracture rates in women with osteoporosis treated with fluoride, and calcium and vitamin D compared with women who received only calcium and vitamin D.[7] This was despite a significant increase in bone mass density of the spine in the fluoride-treated groups. Fluoride regimens consisted of 50 mg enteric-coated sodium fluoride daily, or 150 or 200 mg sodium monofluorophosphate daily. In contrast, a further 4-year study found a decrease in vertebral fracture rates in women with moderate osteoporosis treated with sodium monofluorophosphate 156 mg daily plus calcium compared with those receiving calcium alone.[8]

A systematic review of 11 studies concluded that fluoride can increase bone mineral density at the lumbar spine, but this does not reduce the rate of vertebral fractures.[9] The authors of this review considered that fluoride should not be used in the first-line therapy of postmenopausal osteoporosis.

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4. Pak CYC, *et al.* Slow-release sodium fluoride in the management of postmenopausal osteoporosis: a randomized controlled trial. *Ann Intern Med* 1994; **120:** 625–32.
5. Pak CYC, *et al.* Treatment of postmenopausal osteoporosis with slow-release sodium fluoride: final report of a randomized controlled trial. *Ann Intern Med* 1995; **123:** 401–8.
6. Anonymous. New drugs for osteoporosis. *Med Lett Drugs Ther* 1996; **38:** 1–3.
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8. Reginster JY, *et al.* The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis: a randomized, controlled trial. *Ann Intern Med* 1998; **129:** 1–8.
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Preparations

BP 2008: Sodium Fluoride Mouthwash; Sodium Fluoride Oral Drops; Sodium Fluoride Oral Solution; Sodium Fluoride Tablets;
USP 31: Sodium Fluoride and Acidulated Phosphate Topical Solution; Sodium Fluoride and Phosphoric Acid Gel; Sodium Fluoride Oral Solution; Sodium Fluoride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Elgydium Junior; Elgydium Proteccion; Fluordent; Fluorogel; Fluorogel 2001; Fluoroplat; Naf Buches; Nafluor†; Pentafresh†; ***Austral.:*** Fluor†; Flurets; Neutrafluor; ***Austria:*** Duraphat; Fluodont; Zymafluor; ***Belg.:*** Fluodontyl†; Fluor; Procal†; Z-Fluor; ***Braz.:*** Fluornatrium†; Fluotrat; Primafluor†; ***Canad.:*** Fluor-A-Day; Fluoridrops†; Fluorinse; Fluoritabs†; Fluotic; Karidium†; Oral-B Anti-Cavity Dental Rinse; Oro-NaF; PDF; ***Chile:*** Caristop; Fluocaril Bi-Fluore; Gengisyl; Vitaflur; Vitis Pasta; ***Cz.:*** Fluocaril†; Fluossen†; Ossin†; Zymafluor; ***Denm.:*** Duraphat; Fluorette; ***Fin.:*** Duraphat; Fludent; Fluorilette; ***Fr.:*** Elgydium Junior; Elgydium Protection Caries; Elgyfluor Junior†; Elgyfluor†; Fluodontyl; Fluogum; Fluoplexe; Fluor Microsol†; Fluorex; Sanogyl†; Zymafluor; ***Ger.:*** Duraphat; Fluoretten; Fluoros; NaFril†; Ossin; Zymafluor; ***Gr.:*** Apoflux†; Duraphat; ***Hung.:*** Arthrofluor; Dentocar; Zymafluor; ***India:*** Otoflour; ***Indon.:*** Listermint; ***Israel:*** Denticare†; Dentix; Duraphat; Fluden; Fluvium; Teeth Tough; Zymafluor; ***Ital.:*** AZ Verde; Dentosan Extra Fluor; Dentosan Prevent†; Duraphat; Eburdent; Fluor Verde; Fluor-In; Listerine Difesa; Oral-B Collutorio Protezione Anti-Carie Fluorinse; Zymafluor; ***Mex.:*** Audifluor; ***Neth.:*** Dentigel; En-De-Kay; Osteofluor; Zymafluor; ***Norw.:*** Duraphat; Fluorette; Flux; ***Philipp.:*** Infaflor; ***Pol.:*** Fluossen; Zymafluor; ***Port.:*** Duraphat; Elmex; Fluor-In; Maxfluor; Medusit†; Oratol F†; Zymafluor; ***Rus.:*** Ossin (Оссин)†; ***S.Afr.:*** Listerfluor; Zymafluor; ***Spain:*** Fluodontyl; Fluor; Zymafluor†; ***Swed.:*** Dentan; Dentirol Fluor; Duraphat†; Fludent; Fluorette; Top dent fluor; ***Switz.:*** Duraphat; Fluocaril†; Ossin; Ossofluor; Zymafluor; ***Thai.:*** Zymafluor; ***Turk.:*** Fluoxytil; Zymafluor; ***UK:*** Duraphat; En-De-Kay; Fluor-A-Day; Fluorigard; Sensodyne Mint; ***USA:*** ACT; APF†; Denta Plus; DentaGel; EtheDent; Fluorigard; Fluorinse; Fluoritab; Flura; Karidium; Karigel; Karigel-N; Listerine Tooth Defense; Luride; Minute-Gel; MouthKote F/R; NeutraGard Advanced; OrthoWash; Pediaflor; Pharmaflur; Phos-Flur; Point-Two; Prevident; SF Gel; Thera-Flur.

Multi-ingredient: ***Arg.:*** ADC Fluor; Buclorhex; Cal-C-Vita Fluor; Desensyl; Elgydium; Elgydium Dientes Sensibles; Elgyfluor†; Emoform Total; Esmedent con Fluor; Fluordent PX; Fluorexidina†; Fluorogel 2001 Chiquitos; Fluorogel 2001 para Dientes Sensibles; Hyper Sensitive; Odol Control Sarro†; Odol Med Antiplaca†; Odol Tratamiento de Encias†; Oral-B Dientes Sensibles con Fluor†; Oral-B Enjuague Bucal†; Parodontax Fluor; Sens-Out†; Sensigel; Sensodyne Antisarro; Sensodyne Bicarbonato de Sodio; Sensodyne Proteccion Total; Squam; Tri-Vi-Fluor; ***Austral.:*** Macleans Sensitive; Oral-B Sensitive†; ***Austria:*** Elmex; Ossiplex; ***Belg.:*** Elmex; Fluocaril; Sedemol; Sulfa-Sedemol; ***Braz.:*** Calcifix B12; Calcifix Irradiado; Calcigenol; Calcinol Complexo; Malvatricin; Malvatricin Branqueador; Malvatricin Natural; Poly-Vi-Fluor; Proplax†; Sensodyne Antitartaro; Sensodyne C/Bicarbonato de Sodio; Sensodyne Cool; Sensodyne Fresh Mint; Sensodyne Protecao Total; Tri-Vi-Fluor; ***Canad.:*** Cepacol with Fluoride; Oral Plan†; Oral-B Anti-Bacterial with Fluoride; Oral-B Sensitive†; Sensodyne-F; Tri-Vi-Flor†; ***Chile:*** Cariax; Caristop; FKD; Kariax†; Listermint Con Fluor; Oralgene; Orthokin; Ortodent†; Sensaid; Vitis Encias Pasta; ***Cz.:*** Bifluorid†; Blend-a-Med†; Elmex; Fluocaril Bi-Fluore Vitamin E†; Fluocaril Bi-Fluore†; Natabec F†; Ossiplex†; ***Denm.:*** Bifluorid; ***Fin.:*** Elmex; Xerodent; ***Fr.:*** Elgydium Dents Sensibiles; Elgyfluor†; Elmex Sensitive†; Elmex†; Fluocaril Bi-Fluore; Fluocaril dents sensibles; Fluocaril Junior and Fluocaril Kids; Fluogel; Fluoselgine; Fluosterol; Listerine protection dents et gencives; Parogencyl prevention gencives; Paroplak; Sanogyl Fluo†; Sanogyl Junior†; Sanogyl†; Sensigel; Zymaduo; ***Ger.:*** D-Fluoretten; Elmex; Fluor-Vigantoletten; Lawefluor N†; Multifluorid; Natabec F†; Ossiplex; Ossofortin Plus; Zymafluor D; ***Hong Kong:*** Listerine Teeth and Gum Defence; ***Hung.:*** Elmex; Ossiplex†; ***Israel:*** Elmex; ***Ital.:*** Actifluor†; Actisens†; Aqua Emoform†; AZ Protezione Gengive; AZ Tartar Control; Benodent; Bifluorid†; Broxo al Fluoro; Broxodin†; Colgate Total; Dentosan Junior; Dentosan Placca & Carie; Dentosan Sensibile; Eburdent F; Elmex; Emoform Actisens†; Emoform-Tat†; Eudent con Glysan†; Fluocaril; Fluocaril Bi-Fluore; Lacalut; Oral-B Collutorio per la Protezione di Denti e Gengive; Oral-B Sensitive; Ossiplex†; Otofluor; Plax†; Ridiodent; ***Mex.:*** Fluoxytil; ***Neth.:*** Elmex; ***Norw.:*** Xerodent; ***Philipp.:*** Listerine Teeth & Gum Defense; Poly-Vi-Flor; Xylorinse; ***Pol.:*** Bifluorid; Fluormex; Fluoro-zel; ***Port.:*** Bexident; Biofluor Ortodoncia†; Biofluor Plus†; Biofluor Prevencao†; Biofluor Sensitive†; Fluocaril Bi-Fluore; ***Rus.:*** Elgyfluor (Эльгифлуор); Sensigel (Сенсигель); ***S.Afr.:*** Ossiplex; ***Singapore:*** 2Sensitive†; Elgyfluor; Sensigel; ***Spain:*** Vitagama Fluor; ***Swed.:*** Bifluorid; Xerodent; ***Switz.:*** Elmex; Fluocaril Bi-Fluore†; Paro aux fluorures d'amines Gelee; Parodontax F†; ***Thai.:*** Poly-Vi-Flor; ***Turk.:*** D-Flor; Kalsifluor; Nesgarin; Sensodyne-F Gel; ***UK:*** Dentyl pH; Hydrotab; Listermint with Fluoride; Macleans Mouthguard; Saliva Orthana; Sensodyne-F; ***USA:*** Adeflor M†; Apatate with Fluoride†; ControlRx; Florical; Fluoridex Daily Defense Sensitivity Relief; Mulvidren-F Softab; Poly-Vi-Flor; Polytabs-F; Sensitivity Protection Crest; Soluvite; Tri Vit with Fluoride†; Tri-Vi-Flor; Trivitamin Fluoride Drops; Vi-Daylin/F; ***Venez.:*** Sensodyne.

Sodium Monofluorophosphate

MFP Sodium; Monofluorofosfato sódico; Natrii Monofluorophosphas; Natriummonofluorfosfat; Natriummonofluorifosfaatti; Sodium Fluorophosphate. Disodium phosphorofluoridate.

Na_2PO_3F = 143.9.

CAS — 10163-15-2.

ATC — A01AA02; A12CD02.

ATC Vet — QA01AA02; QA12CD02.