Carthamus tinctorius. It contains not less than 1% of total flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4), calculated with reference to the dried drug. Protect from light.

Ph. Eur. 6.2 (Safflower Oil, Refined). The fatty oil obtained from seeds of *Carthamus tinctorius* (type I) or from seeds of hybrids of *C. tinctorius* (type II), by expression and/or extraction followed by refining. Type II refined safflower oil is rich in oleic acid. It may contain a suitable antoxidant. A clear, viscous, yellow to pale yellow liquid. Relative density about 0.922 (type I) and about 0.914 (type II). Practically insoluble in alcohol; miscible with petroleum spirit (b.p.: 40° to 60°). Store in well-filled airtight containers. Protect from light.

USP 31 (Safflower Oil). The refined fixed oil yielded from the seed of *Carthamus tinctorius* (Compositae). A light yellow oil. It thickens and becomes rancid on prolonged exposure to air. Insoluble in water; miscible with chloroform and with ether. Store in airtight containers. Protect from light.

Profile

Safflower oil is the refined fixed oil obtained from the seeds of the safflower, or false (bastard) saffron, *Carthamus tinctorius* (Compositae). It contains about 75% of linoleic acid as well as various saturated fatty acids.

Safflower oil has similar actions and uses to those of soya oil, p.1965. Emulsions containing a mixture of safflower oil 5% and soya oil 5%, or 10% and 10% respectively, are given as part of total parenteral nutrition regimens.

Adverse effects. For reference to the association of safflower oil-based emulsion, as part of a parenteral nutrition regimen, with the development of sinus bradycardia, see Effects on the Cardiovascular System, under Soya Oil, p.1966.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lipidos†.

Multi-ingredient: ***Canad.:*** Microlipid; ***Chile:*** Liposyn†; ***Denm.:*** Liposyn†; ***Fin.:*** Liposyn†; ***Ger.:*** Abbolipid†; ***Israel:*** Liposyn; ***Ital.:*** Liposyn†; ***Mex.:*** Liposyn; ***Swed.:*** Liposyn†; ***Switz.:*** A Vogel Capsules polyvitamineés†; ***Turk.:*** Liposyn; ***USA:*** Liposyn II; Microlipid.

Selenium

Selen; Selenio; Sélénium.

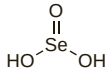
Se = 78.96.

Selenious Acid

Kwas selenawy; Selenioso, ácido. Monohydrated selenium dioxide .

H_2SeO_3 = 129.0.

CAS — 7783-00-8.



Pharmacopoeias. In *US*.

USP 31 (Selenious Acid). Store in airtight containers.

Potassium Selenate

Selenato potásico.

K_2SeO_4 = 221.2.

CAS — 7790-59-2.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Potassium Selenate). Colourless crystals or a white crystalline powder. Freely soluble in water.

Sodium Selenate

Disodium Selenate; Natriumseleniat; NSC-378348; Selenato sódico; Sodium Selenium Oxide.

Na_2SeO_4 = 188.9.

CAS — 13410-01-0.

ATC — A12CE01.

ATC Vet — QA12CE01.

Sodium Selenite

Natrii selenis pentahydricus; Natrio selenitas pentahidratas; Natriumseleniittipentahydraatti; Natriumselenitpentahydrat; Seleničitan sodný pentahydrát; Selenito sódico; Sodium (sélénite de) pentahydraté; Sodu selenin pięciowodny; Sodyum Selenit.

$Na_2SeO_3.5H_2O$ = 263.0.

CAS — 10102-18-8.

ATC — A12CE02.

ATC Vet — QA12CE02.

Pharmacopoeias. In *Eur.* (see p.vii). *BP(Vet)* includes anhydrous sodium selenite.

Ph. Eur. 6.2 (Sodium Selenite Pentahydrate). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

BP(Vet) 2008 (Sodium Selenite). A white to slightly greyish pink granular powder. Freely soluble in water; practically insoluble in alcohol and ether.

Adverse Effects

Overdosage of selenium has been associated with loss of hair, nail changes, diarrhoea, dermatitis, metallic taste, garlic odour of breath, irritability, fatigue, and peripheral neuropathy.

Effects on mortality. A systematic review[1] of the effect of antoxidant supplements on mortality in randomised primary and secondary prevention studies considered that selenium had no significant effect on mortality, either beneficial or harmful; however, it was recommended that future studies should be monitored closely for harm.

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).

Toxicity. *Chronic* exposure to high amounts of selenium has been reported to cause toxic effects on endocrine function, hepatotoxicity, gastrointestinal disturbances, and dermatological effects such as nail and hair loss and dermatitis. There has been some suggestion also of neurotoxicity, and a possible increased risk of amyotrophic lateral sclerosis. Studies have had conflicting results, and different inorganic and organic forms may vary greatly in biological activity, toxicity, and nutritional importance.[1]

Acute toxicity has also been reported; characteristic symptoms of selenium toxicity are garlicky or sour breath odour, vomiting and gastrointestinal disturbances, restlessness, hypersalivation, muscle spasms, haemolysis, liver necrosis, cerebral and pulmonary oedema, coma, and death.[1-3] A man who had taken vitamin tablets containing between 500 and 1000 times the amount of selenium labelled on the bottle developed generalised alopecia, changes in nail colour, diarrhoea, worsening fatigue, and paraesthesias. Two weeks after stopping the vitamins, early regrowth of hair and yellowish-white and red transverse lines on his nails were noted.[2] In another case, an elderly man who was concerned that he might have prostate cancer ingested 10 g of sodium selenite. He developed significant abdominal pain, vomiting and diarrhoea, hypotension, and ventricular tachycardia. Blood tests showed acidosis, hypokalaemia and an excessive selenium concentration. Despite symptomatic therapy, he suffered a cardiac arrest and died.[3]

1. Vinceti M, *et al.* Adverse health effects of selenium in humans. *Rev Environ Health* 2001; **16:** 233–51.
2. Clark RF, *et al.* Selenium poisoning from a nutritional supplement. *JAMA* 1996; **275:** 1087–8.
3. See KA, *et al.* Accidental death from acute selenium poisoning. *Med J Aust* 2006; **185:** 388–9.

Pharmacokinetics

Selenium compounds are generally readily absorbed from the gastrointestinal tract. Selenium is stored in red blood cells, the liver, spleen, heart, and nails. It is converted in tissues to its metabolically active forms. Selenium is excreted in the urine, and to a lesser extent in the faeces.

Uses and Administration

Selenium is an essential trace element. It is an integral part of the enzyme system glutathione peroxidase, which protects intracellular structures against oxidative damage. Deficiency of selenium has been associated with an endemic form of cardiomyopathy, Keshan disease, seen in certain areas of China. It has also been associated with Kaschin-Beck disease, an endemic osteoarthropathy, which causes a severe deformity of the joints. Selenium is present in foods mainly as the amino acids selenomethionine and selenocysteine and derivatives.

Selenious acid and its sodium salt, sodium selenite, are used as a source of selenium, especially for patients with deficiency states after prolonged parenteral nutrition. Suggested doses for addition to total parenteral nutrition are 31.5 micrograms elemental selenium daily for adults and children greater than 40 kg, and 2 micrograms/kg daily for infants and children to a maximum of 30 micrograms daily. Sodium selenate has also been used.

For proven selenium deficiency that cannot be offset from food sources, selenium may be given orally, or by intramuscular or intravenous injection, usually in the form of sodium selenite pentahydrate, to provide doses of about 100 to 200 micrograms selenium daily; if necessary this can be increased to 500 micrograms daily.

Selenate and selenite salts are used for selenium deficiency states in veterinary medicine.

Action. References.

1. Rayman MP. The importance of selenium to human health. *Lancet* 2000; **356:** 233–41.

Administration in neonates. The low selenium plasma concentrations in preterm neonates have been suggested to be a potential risk factor for neonatal respiratory disorders and retinopathy of prematurity. A systematic review[1] found that supplementation with selenium did not reduce the incidence of these complications, nor is it associated with improved survival. However, it is associated with benefit in terms of reduction in the number of episodes of late-onset sepsis in very preterm infants. There was evidence that recommended doses in this group might be inadequate for some populations.

1. Darlow BA, Austin NC. Selenium supplementation to prevent short-term morbidity in preterm neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 10/11/05).

HIV infection and AIDS. A randomised controlled study found that oral supplementation with selenium 200 micrograms daily for 9 months suppressed the progression in HIV-1 viral load and provided indirect improvement of the CD4 count.[1] For a study reporting increased CD4 and CD8 counts, but increased genital HIV-1 shedding with multivitamin plus selenium supplementation, see HIV Infection and AIDS, p.1926.

1. Hurwitz BE, *et al.* Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. *Arch Intern Med* 2007; **167:** 148–54.

Human requirements. In the UK dietary reference values (see p.1925)[1] and in the USA recommended dietary allowances (RDA)[2] have been published for selenium.

In the UK the reference nutrient intake for adults is 75 and 60 micrograms daily for men and women respectively; values are also given for infants and children of varying ages and for lactating women. The UK report also noted that there was no convincing evidence that high intakes protected against cancer or cardiovascular disease; indeed, there was even some evidence that high intakes disturbed selenium homoeostasis and it was recommended that the maximum safe intake from all sources should be set at 450 micrograms daily for adult males. The Expert Group on Vitamins and Minerals[3] have since established a safe upper level (SUL) for selenium of 450 micrograms daily.

In the USA, the RDA for adult males and females is 55 micrograms daily, and again values are also given for infants and children as well as pregnant and lactating women. The tolerable upper intake level is 400 micrograms daily.[2]

WHO have recommended a lower limit of the safe range of population mean intakes of dietary selenium of 40 micrograms daily for adult males and 30 micrograms daily for adult females.[4] A maximum daily safe dietary selenium intake of 400 micrograms was suggested for adults.

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 C, vitamin E, selenium, and carotenoids.* Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (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 10/11/05)
4. WHO. Selenium. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996; 105–22.

Prophylaxis of malignant neoplasms. Selenium supplementation did not protect against the development of new basal or squamous cell carcinomas of the skin in a study of patients with a history of these cancers.[1] Further follow-up data[2] showed a statistically significant increased risk of squamous cell carcinoma and of total non-melanoma skin cancer with selenium supplementation. However, analysis of secondary end-points at the first report indicated a reduced incidence of various other cancers in this study group.[1]

Subsequent study has suggested, in particular, an association between low selenium intake and the risk of prostate cancer; incidence was reduced by 63% in patients receiving the supplement.[3] Further follow-up confirmed this inverse association, but found that only men with low baseline selenium concentrations were likely to benefit.[4] Another group has also reported an inverse correlation between surrogate measurements of long-term selenium intake and the risk of advanced prostate cancer.[5] A case-control study[6] found an inverse association between pre-diagnostic plasma selenium concentrations and the subsequent risk of advanced prostate cancer, but not of localised prostate cancer. Higher pre-diagnostic selenium levels were associated with a lower risk of prostate cancer only for subjects with increased baseline prostate-specific antigen (PSA) concentrations (above 4 nanograms/mL). The authors hypothesised that selenium may influence tumour progression. Trials of selenium supplementation with prostate cancer detection as primary end-points are ongoing.

Similarly, an inverse association between selenium concentrations and the risk of bladder cancer has been reported, although results from case-control studies are inconsistent. Controlled studies investigating the effect of selenium on bladder cancer recurrence and prognosis are planned.[7]

For a finding that selenium supplementation had no beneficial effect on overall mortality, see Effects on Mortality, above.

1. Clark LC, *et al.* Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA* 1996; **276:** 1957–63. Correction. *ibid.* 1997; **277:** 1520.
2. Duffield-Lillico AJ, *et al.* Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst* 2003; **95:** 1477–81.
3. Clark LC, *et al.* Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998; **81:** 730–4.
4. Duffield-Lillico AJ, *et al.* Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int* 2003; **91:** 608–12.

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.

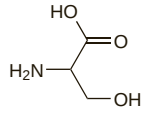
Serine *(USAN, rINN)*

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.

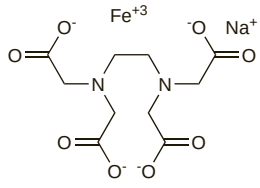
Натрия Фередетат

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