Ferrous Gluconate

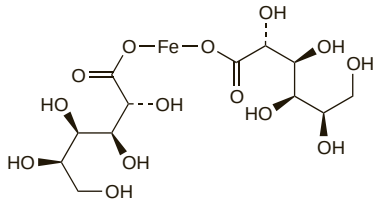
E579; Eisen(II)-Gluconat; Ferroglukonaatti; Ferroglukonat; Ferrosi gluconas; Ferrosi Gluconas Hydricus; Ferroso, gluconato; Geležies(II) gliukonatas; Gluconate ferreux; Glukonan železnatý hydrát; Vas(II)-glükonát; Železa(II) glukonian. Iron (II) di(D-gluconate).

$C_{12}H_{22}FeO_{14}.xH_2O$.

CAS — 299-29-6 (anhydrous ferrous gluconate); 12389-15-0 (ferrous gluconate dihydrate).

ATC — B03AA03.

ATC Vet — QB03AA03.



(anhydrous ferrous gluconate)

Pharmacopoeias. In *Eur.* (see p.vii).
Chin. and *US* specify the dihydrate.
Ph. Eur. 6.2 (Ferrous Gluconate). A greenish-yellow to grey powder or granules. It contains not less than 11.8% and not more than 12.5% of ferrous iron calculated with reference to the dried substance. Freely but slowly soluble in water producing a greenish-brown solution, more readily soluble in hot water; practically insoluble in alcohol. A 10% solution in water has a pH of 4.0 to 5.5 three to four hours after preparation. Protect from light.
USP 31 (Ferrous Gluconate). A yellowish-grey or pale greenish-yellow, fine powder or granules having a slight odour resembling that of burnt sugar. Soluble 1 in 5 of water; practically insoluble in alcohol. A 5% solution in water is acid to litmus. Store in airtight containers.

Profile

Ferrous gluconate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 1.8 g daily (equivalent to up to 210 mg of iron daily).

Preparations

BP 2008: Ferrous Gluconate Tablets;
USP 31: Ferrous Gluconate Capsules; Ferrous Gluconate Elixir; Ferrous Gluconate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Fergon†; ***Austria:*** Losferron; ***Belg.:*** Losferron; ***Canad.:*** Novo-Ferrogluc; ***Chile:*** Glucoferro K; ***Cz.:*** Losferron; ***Ger.:*** Eisen-Sandoz; Ferrum Verla; Losferron; Rulofer G; Vitaferro; ***Israel:*** Ferro; Ferro-Nes; ***Ital.:*** Auxofer; Bioferal; Bioglufer; Blizer; Blustark; Crom; Cromatonferro; Effegyn; Emonorm†; Emoxiron; Eriglobin; Eritropiu; Ferig; Ferro Complex; Ferrogyn; Flexifer†; Gloros; Glucoferro; Losferron; Megafer; Monoferro; Prontoferro; Sidervim; Sustemial; ***Neth.:*** Losferron; ***NZ:*** Fergon†; ***Pol.:*** Ascofer; ***Port.:*** Anemital†; Bioferro; Hemototal; Losferron†; ***Rus.:*** Ferronal (Ферронал); ***Spain:*** Ferrum Sandoz; Losferron; ***Switz.:*** Loesfer†; Lufer; ***Turk.:*** Losferron; ***USA:*** Fergon; ***Venez.:*** Ferroper†; Irolen†; Salfer; Yisafer.

Multi-ingredient: ***Austria:*** Losferron-Fol; ***Fr.:*** Tot'Hema; ***Ger.:*** Biovital Aktiv†; Ferro-C-Calcium; Ferrodix†; Floradix Krauterblut; ***India:*** Elferri†; Gynae-CVP; JP Tone; Livogen Hemtonic; Pentavite†; ***Indon.:*** Adfer; Biosanbe; Diabion; Emibion; Habebion; Inbion; Maltiron; Muveron; Neogobion; Opibion; Sangobion; Sangofer; Sangovitin; Tropifer; Vitabion; ***Malaysia:*** Sangobion; ***Philipp.:*** Sangobion; ***Pol.:*** Additiva Ferrum; ***Port.:*** Tot'Hema; ***Rus.:*** Tot'Hema (Тотема); ***S.Afr.:*** Kiddie Vite†; ***Singapore:*** Neogobion; Sangobion; ***Spain:*** Clamarvit†; ***Switz.:*** Duofer; Duofer Fol; Ferrascorbin; ***Thai.:*** Ferro-Be-Sian; Glufer-C; ***Turk.:*** Ferro-Vital; ***UK:*** Foresight Iron Formula; ***USA:*** Compete; Ferralet Plus†; Hytinic†; Iromin-G; Mission Surgical Supplement†; ***Venez.:*** Gestocal†.

Ferrous Glycine Sulfate

Demir Glisin Sülfat; Ferroglycini Sulfas; Ferroglycinsulfat; Ferroglysiinisulfaatti; Ferroso de glicina, sulfato; Ferrous Aminoacetosulphate; Ferrous Glycine Sulphate.

CAS — 14729-84-1.

ATC — B03AA01.

ATC Vet — QB03AA01.

Profile

Ferrous glycine sulfate is a chelate of ferrous sulfate and glycine used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses containing the equivalent of up to 150 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Neutrofer; ***Chile:*** Cheltin; ***Denm.:*** Glycifer; Niferex; ***Fin.:*** Obsidan; ***Ger.:*** Ferro Sanol; Ferro sanol duodenal; ***Gr.:*** Ferro Sanol; ***Irl.:*** Plesmet; ***Port.:*** Ferrocutid†; Niferex; ***Spain:*** Ferbisol; Ferro Sanol; Glutaferro; ***Swed.:*** Niferex; ***Switz.:*** Ferrosanol duodenal; ***Turk.:*** Ferro Sanol; ***UK:*** Plesmet†; ***USA:*** Gentle Iron; ***Venez.:*** Herronduo.

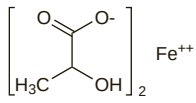
Multi-ingredient: ***Braz.:*** Neutrofer Folico; ***Fin.:*** Obsidan comp; ***Ger.:*** Ferro sanol comp; Ferro sanol gyn; ***India:*** Fecontin-F; Fecontin-Z; ***Turk.:*** Ferro Sanol B; ***USA:*** Repliva; ***Venez.:*** Herrongyn.

Ferrous Lactate

E585; Ferroso, lactato; Iron Lactate.

$C_6H_{10}FeO_6.3H_2O$ = 288.0.

CAS — 5905-52-2 (anhydrous ferrous lactate); 6047-24-1 (ferrous lactate trihydrate).



(anhydrous ferrous lactate)

Profile

Ferrous lactate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cromatonbic Ferro†; ***S.Afr.:*** Ferro Drops L; ***Spain:*** Cromatonbic Ferro.

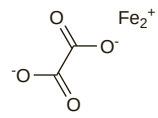
Multi-ingredient: ***Hung.:*** Fagifor†.

Ferrous Oxalate

Ferroso, oxalato; Ferrum Oxalicum Oxydulatum; Iron Protoxalate.

$C_2FeO_4.2H_2O$ = 179.9.

CAS — 516-03-0 (anhydrous ferrous oxalate); 6047-25-2 (ferrous oxalate dihydrate).



(anhydrous ferrous oxalate)

Profile

Ferrous oxalate has been used as a source of iron (p.1949).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Disulone.

Ferrous Succinate

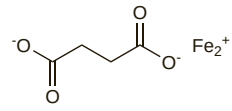
Ferroso, succinato.

$C_4H_4FeO_4$ = 171.9.

CAS — 10030-90-7.

ATC — B03AA06.

ATC Vet — QB03AA06.



Profile

Ferrous succinate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to about 600 mg daily (equivalent to up to about 200 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferdromaco; ***Ger.:*** Ferrlecit 2; ***Swed.:*** Ferromyn S.

Multi-ingredient: ***India:*** Hematrine.

Ferrous Sulfate

Demir Sülfat; Eisen(II)-Sulfat; Ferreux (Sulfate); Ferrosi Sulfas; Ferrosi sulfas heptahydricus; Ferroso, sulfato; Ferrosulfaattiheptahydraatti; Ferrosulfatheptahydrat; Ferrous Sulphate; Ferrum Sulfuricum Oxydulatum; Geležies(II) sulfatas heptahidratas; Iron (II) Sulphate Heptahydrate; Iron Sulphate; Síran železnatý heptahydrát; Sulfate ferreux heptahydraté; Vas(II)-szulfát; Železa(II) siarczan.

$FeSO_4.7H_2O$ = 278.0.

CAS — 7720-78-7 (anhydrous ferrous sulfate); 7782-63-0 (ferrous sulfate heptahydrate).

ATC — B03AA07.

ATC Vet — QB03AA07; QB03AD03.

NOTE. Crude ferrous sulfate is known as Green Vitriol or Green Copperas.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Swiss also includes ferrous sulfate sesquihydrate.
Ph. Eur. 6.2 (Ferrous Sulphate Heptahydrate). A light green crystalline powder or bluish-green crystals, efflorescent in air. It is oxidised in moist air, becoming brown. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.
USP 31 (Ferrous Sulfate). Pale bluish-green, odourless, crystals or granules. It is efflorescent in dry air and oxidises readily in moist air to form brownish-yellow basic ferric sulfate. Soluble 1 in 1.5 of water and 1 in 0.5 of boiling water; insoluble in alcohol. A 10% solution in water is acid to litmus, having a pH of about 3.7. Store in airtight containers.

Dried Ferrous Sulfate *(USAN)*

Dried Ferrous Sulphate; Exsiccated Ferrous Sulphate; Ferreux (sulfate) desséché; Ferrosi sulfas desiccatus; Ferrosi Sulfas Exsiccatus; Ferroso desecado, sulfato.

CAS — 13463-43-9.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Ferrous Sulphate, Dried). Hydrated ferrous sulphate deprived of part of its water of hydration by drying. A greyish-white powder which is oxidised in moist air, becoming brown. It contains 86.0 to 90.0% of $FeSO_4$. Slowly but freely soluble in water, very soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.
USP 31 (Dried Ferrous Sulfate). A greyish-white to buff-coloured powder consisting primarily of ferrous sulfate monohydrate with varying amounts of ferrous sulfate tetrahydrate. It contains 86.0 to 89.0% of $FeSO_4$. Slowly soluble in water; insoluble in alcohol.

Profile

Ferrous sulfate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally; the dried form is often used in solid dosage forms and the heptahydrate in liquid dosage forms. Usual doses of dried ferrous sulfate are up to 600 mg daily (equivalent to 180 to 195 mg of iron daily, this figure being somewhat variable depending on the purity and water content of the salt).

Ferrous sulfate oxidised with nitric and sulfuric acids yields ferric subsulfate solution, also known as Monsel's solution, which has been used as a haemostatic.

Preparations

BP 2008: Ferrous Sulphate Tablets; Paediatric Ferrous Sulphate Oral Solution; Prolonged-release Ferrous Sulphate Tablets;
BPC 1973: Compound Ferrous Sulphate Tablets;
USP 31: Ferric Subsulfate Solution; Ferrous Sulfate Oral Solution; Ferrous Sulfate Syrup; Ferrous Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Eurofer; Factofer; Feklon; Fer-In-Sol; Ferlea†; Ferricol; Ferrocebrina; Ferromas; Ferrometion; Hemoferrol; Iberol; Medifer; Siderblut; Vitaferro†; ***Austral.:*** Ferro-Gradumet; Ferrograd C; ***Austria:*** Aktiferrin; Ferro-Gradumet; Ferrograd C; Infa-Tardyferon; Tardyferon; ***Belg.:*** Fero-Grad; Fero-Gradumet; ***Braz.:*** Anemiplus†; Cimefer; Fer-In-Sol; Ferrison†; Ferronil; Ferrosol; Ferrototal; Ferrotron†; Hematofer†; Iberol; Ironfer; Lomfer†; Neck-Fer†; Perfer†; Salonfer†; Sulfatofer†; Sulfer Plus; Sulfergan Composto; Sulferro; Sulferrol; Tratfer†; ***Canad.:*** Fer-In-Sol; Fero-Grad; Ferodan; Ferofate; Slow-Fe; ***Chile:*** Ferinsol; Ferrigot; Ferromalt; Iberol Simple†; ***Cz.:*** Aktiferrin; Eisen-Diasporal†; Ferro-Gradumet†; Sorbifer; Tardyferon; ***Denm.:*** Ferro; ***Fin.:*** Duroferon; Retafer; ***Fr.:*** Fero-Grad vitamine C; Timoferol; ***Ger.:*** Aktiferrin N; Ceferro; Dreisafer; Eisendragees-ratiopharm; Eryfer; Ferrogamma; FERROinfant N†; Haemoprotect; Hamatopan; Kendural C; Plastufer; Plastulen; Tardyferon; Vitaferro; ***Gr.:*** Fer-In-Sol†; Microfer; Resoferon; Tardyferon; ***Hong Kong:*** Feospan†; Ferasul; Iron-200; ***Hung.:*** Aktiferrin; Ferro-Gradumet; Sorbifer; Tardyferon; ***Irl.:*** Feospan; Fer-In-Sol; Ferrograd; Ferrograd C; ***Israel:*** Ferro-Gradumet; Slow-Fe; ***Ital.:*** Fer-In-Sol; Ferrograd; Ferrograd C; ***Malaysia:*** Feospan†; Retafer; ***Mex.:*** Fer-In-Sol; Ferifer; Forcil; Hemobion; Valdefer; ***Neth.:*** Fero-Gradumet; Ferrograd; Protiferron; ***Norw.:*** Duroferon; Ferromax; Nycoplus Ferro-Retard; ***NZ:*** Ferro-Gradumet; Ferrograd C; ***Philipp.:*** Feosol; Feovit; Fer-In-Sol; Ferglobin; Ferosal; Sorbifer; United Home Fersulfate Iron; ***Pol.:*** Ferro-Gradumet; Hemofer; Sorbifer; Tardyferon; ***Port.:*** Ferro-Gradumet; Tardyferon; ***Rus.:*** Aktiferrin (Актиферрин); Ferro-Gradumet (Феррогрaдумет); Ferroplex (Ферроплекс); Hemofer (Гемофер); Sorbifer (Сорбифер); Tardyferon (Тардиферон); ***S.Afr.:*** Fero-Grad; Fesofor; ***Singapore:*** Feospan†; ***Spain:***

Fero-Gradumet; Tardyferon; ***Swed.:*** Duroferon; ***Switz.:*** Actiferrine; Ferro-Gradumet; Resoferon†; ***Thai.:*** Fer-In-Sol; Ferrotabs; Pediron; ***Turk.:*** Oroferon; Tardyferon; ***UAE:*** Kdiron; ***UK:*** Feospan; Ferrograd; Ferrograd C; Ironorm; Slow-Fe†; ***USA:*** Ed-in-Sol†; Fe ; Feosol; Fer-gen-sol; Fer-In-Sol; Fer-Iron†; Feratab; Fero-Grad; Irospan; Slow-Fe; ***Venez.:*** Corsafer†; Fer-In-Sol; Gotafer†; Ironcor†; Mol-Iron†.

Multi-ingredient: ***Arg.:*** Factofer B12; Fefol; Ferro Folic; Hierro Plus; Iberol; Rubiron; Sideralce; Vifortol Prenatal; ***Austral.:*** Fefol; FGF Tabs; Irontona; ***Austria:*** Aktiferrin Compositum; Ferrograd Fol; Ferrum-Quarz; Kephalodoron; Tardyferon-Fol; ***Braz.:*** Anemix†; Anemofer†; Betozone; Cobaldoze; Combiron; Coraben†; Dobiron; Ferrocomplex; Ferroplex; Ferrotonico B12†; Ferrotonico†; Ferrotrat; Iberin Folico; Iberol; Novofer; Paratonico; Rubrargil; Sulfato Ferroso Composto; Sulfatofer†; Tonico Blument†; ***Canad.:*** Iberet†; Slow-Fe Folic; ***Chile:*** Acomir con hierro; Ferranem; Ferro F-500 Gradumet†; Iberol; Iberol Folico; ***Cz.:*** Aktiferrin Compositum; Ferro-Folgamma; Ferrograd Folic†; Tardyferon-Fol; ***Fr.:*** Tardyferon; Tardyferon B ; ***Ger.:*** Biovital Aktiv†; Eisenkapseln†; Eryfer comp; Ferro-Folgamma; Ferro-Folsan; Hamatopan F; Kendural-Fol-500; Plastulen N; Tardyferon-Fol; ***Gr.:*** Feofol; Fero-Folic; Gyno-Tardyferon; ***Hong Kong:*** Iberet; Iberet-Folic; ***Hung.:*** Biovital†; Ferro-Folgamma; Ferrograd Folic; Tardyferon-Fol; ***India:*** Cofol; Conviron-TR; Fefol; Fefol-Z; Ferrochelate-Z; Fesovit; Iberol; JP Tone-TR; Maxiferon; Plastules; ***Indon.:*** Iberet; Iberet-Folic; ***Irl.:*** Fefol; Ferrograd Folic; Ferrotab†; ***Israel:*** Aktiferrin-F; Ferrograd Folic; Slow-Fe Folic; ***Ital.:*** Ferrograd Folic; ***Malaysia:*** Aktiferrin-F; Iberet-Folic; Iberet†; ***Mex.:*** Ferro Folico; Iberet; Iberol; Orafer Comp; Tardyferon-Fol; ***NZ:*** Ferrograd Folic; ***Philipp.:*** Ameciron; Appebon with Iron; Appetason; Drexabion OB; Dupharon; Femina; Ferlin; Ferosal; Ferro-Folsan Plus; Foralivit; IBC; Iberet; Iberet-Folic; Imefer; Irobon; Magniferron; Mediferron-Vita; Micron-C; Molvite with Iron; Propan with Iron; Regeron-E Plus; Terraferron; ***Pol.:*** Ferrograd Folic; Hemofer F; Tardyferon-Fol; ***Port.:*** Ferro-Folsan†; Ferrograd Folico; Folifer; Tardyferon-Fol; ***Rus.:*** Aktiferrin Compositum (Актиферрин Композитум); Fenules (Фенюльс); Ferro-Folgamma (Ферро-Фольгамма); Gyno-Tardyferon (Гино-тардиферон); ***S.Afr.:*** Fefol; Fefol-Vit; Fero-Folic; Ferrous Sulphate Compound; Foliglobin; ***Singapore:*** Aktiferrin-F; Ferbeaplex; Iberet; Iberet-Folic; Tardyferon B †; ***Switz.:*** Actiferrine-F Nouvelle formule; Fero-Folic; Gyno-Tardyferon; Kendural; Tardyferon; ***Thai.:*** Iberet†; ***Turk.:*** Gyno-Tardyferon; Gynoferon; Natabec; ***UAE:*** Folicron; ***UK:*** Fefol; Ferrograd Folic; Ironorm; Slow-Fe Folic†; ***USA:*** Aqua Ban Plus; Fero-Folic; Generet; Gerivites†; Iberet-Folic†; Iberet†; Slow Fe with Folic Acid; ***Venez.:*** Autrin†; Ferro-Folic; Ferroce con B12.

Ferrous Tartrate

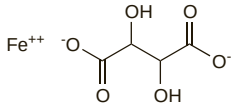
Ferrosi Tartras; Ferroso, tartrato.

$C_4H_4FeO_6,2H_2O$ = 249.0.

CAS — 2944-65-2 (anhydrous ferrous tartrate).

ATC — B03AA08.

ATC Vet — QB03AA08.



(anhydrous ferrous tartrate)

Profile

Ferrous tartrate has been used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Denm.:*** Ferroplex-frangula.

Ferumoxytol *(USAN)*

Code 7228.

Ферумокситол

CAS — 1309-38-2.

Profile

Ferumoxytol is a superparamagnetic iron oxide that is coated with a low-molecular-weight semisynthetic carbohydrate, polyglucose sorbitol carboxymethyl ether. It is under investigation as a source of iron for iron-deficiency anaemia in patients with chronic kidney disease. Ferumoxytol may potentially be used as a contrast medium in magnetic resonance imaging (p.1474).

◊ References.

1. Landry R, *et al.* Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *Am J Nephrol* 2005; **25:** 400–10.
2. Spinowitz BS, *et al.* The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients. *Kidney Int* 2005; **68:** 1801–7.

Folic Acid *(BAN, rINN)*

Acide folique; Ácido fólico; Acidum folicum; Folacin; Folik Asit; Folinsyre; Folio rūgštis; Folsav; Folsyra; Foolihappo; Kwas foliowy; Kyselina listová; PGA; Pteroylglutamic Acid; Pteroylmonoglutamic Acid; Vitamin B_9; Vitamin B_{11}. *N*-[4-(2-Amino-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L(+)-glutamic acid.

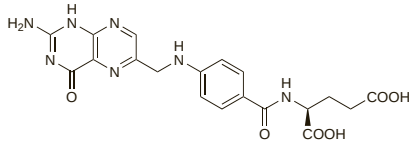
Фолиевая Кислота

$C_{19}H_{19}N_7O_6$ = 441.4.

CAS — 59-30-3 (folic acid); 6484-89-5 (sodium folate).

ATC — B03BB01.

ATC Vet — QB03BB01.



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

Ph. Eur. 6.2 (Folic Acid). A yellowish or orange crystalline powder. Practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions. Protect from light.

USP 31 (Folic Acid). A yellow, yellow-brownish, or yellowish-orange, odourless crystalline powder. Very slightly soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether. It readily dissolves in dilute solutions of alkali hydroxides and carbonates; soluble in hot, 3N hydrochloric acid and in hot, 2N sulfuric acid; soluble in hydrochloric acid and in sulfuric acid, yielding pale yellow solutions. Protect from light.

Adverse Effects

Folic acid is generally well tolerated. Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely.

Hypersensitivity. A woman had 3 episodes of hypersensitivity, including anaphylaxis, on exposure to synthetic folic acid. Intradermal testing with folic acid solution was positive and a blinded challenge to folic acid solution led to widespread urticaria. Sensitisation to folic acid may have occurred after supplementation with vitamin B, at which time she had recurrent episodes of urticaria. The patient appeared to tolerate dietary folates, and the authors suggested that foods fortified with folic acid be clearly labelled.[1]

1. Smith J, *et al.* Recurrent anaphylaxis to synthetic folic acid. *Lancet* 2007; **370:** 652.

Precautions

Folic acid should never be given alone or with inadequate amounts of vitamin B_{12} for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B_{12} deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage, such as subacute combined degeneration of the spinal cord (see also Vitamin B_{12} Deficiency, below).

Breast feeding. Folic acid is excreted into breast milk. No adverse effects have been observed in breast-fed infants whose mothers were receiving folic acid, and the American Academy of Pediatrics considers that it is therefore usually compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/01/06)

Carcinogenicity. Follow-up data from a large study of folate supplementation suggested a greater risk of death due to breast cancer in those women randomised to high doses; the association was not statistically significant and further studies were considered necessary.[1] In contrast, other studies suggest a reduced risk of some cancers with folate supplementation, see Prophylaxis of Malignant Neoplasms, p.1927. A large study found that folic acid supplementation did not reduce colorectal adenoma risk; evidence for an increased risk of adenomas with supplementation was equivocal.[2] *Animal* studies suggest that folic acid may have dual modulatory effects on carcinogenesis, depending on dose and timing of supplementation. Folate deficiency may inhibit, whereas supplementation may promote, the progression of established neoplasms. In normal tissue, however, folate deficiency can predispose towards neoplastic transformation and modest amounts of folate may suppress tumour development; supraphysiological doses may enhance tumour progression.[3,4] Thus, use of folate before the existence of preneoplastic lesions may prevent tumour development, whereas use once early lesions are established appears to increase tumorigenesis.[5] However, determining the presence of preneoplastic foci in the general population is almost impossible.[4] Given the tendency for cancer patients to consume more supplements than healthy subjects, the possibility of adverse effects of folic acid on cancer progression, recurrence, and metastasis should be borne in mind, and research on folate supplementation among patients with cancer is needed.[5] Careful monitoring of the long-term effects of folic acid food fortification is also advised,[3,4] and some have advocated against mandatory fortification on this basis.[6]

1. Charles D, *et al.* Taking folate in pregnancy and risk of maternal breast cancer. *BMJ* 2004; **329:** 1375–6.
2. Cole BF, *et al.* Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007; **297:** 2351–9.
3. Kim Y-I. Will mandatory folic acid fortification prevent or promote cancer? *Am J Clin Nutr* 2004; **80:** 1123–8.
4. Kim Y-I. Folate: a magic bullet or a double edged sword for colorectal cancer prevention? *Gut* 2006; **55:** 1387–9.
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Vitamin B_{12} deficiency. The issue of fortification of food with folic acid to reduce the number of infants born with neural tube defects (see below) has created debate[1-7] on the amount of fortification and on the risks of masking vitamin B_{12} deficiency, particularly in the elderly. As mentioned in Precautions, above, it is accepted that folic acid should not be used in megaloblastic anaemia due to vitamin B_{12} deficiency, because it will not prevent the neurological manifestations of this deficiency, and may delay the diagnosis. Masking of vitamin B_{12} deficiency has been noted with daily doses of folic acid of 5 mg, and it is generally considered that very low doses do not have this effect. It has also been stated that folic acid may precipitate the neurological manifestations of vitamin B_{12} deficiency; however, a review of the evidence suggests this is unlikely.[8]

Nevertheless, concerns regarding neurological effects of vitamin B_{12} deficiency in the elderly have led to adoption of a level of folic acid fortification in the USA that is accepted will not provide optimum protection against neural tube defects, but that is hoped will minimise any risks.[9] It has been suggested that fortification with vitamin B_{12} as well might also be a solution.[10-12] While some studies of food fortification show no evidence of a deterioration in vitamin B_{12} status in elderly patients,[13,14] there is concern[12,15] that individuals may be consuming folic acid in excess of the upper limit of 1 mg daily (see under Human Requirements, below). Because several countries in the Americas fortify flour, but at varying levels, a technical consultation was convened by the Pan American Health Organization, the March of Dimes, and the CDC, in order to develop guidelines on fortification.[15] It was recommended[16] that all women of reproductive age consume 400 micrograms daily of synthetic folic acid in addition to dietary intake; a minimum additional intake of 200 micrograms daily of folic acid from fortified foods was proposed. A target mean intake of 1 microgram daily of vitamin B_{12} from food fortification was recommended in countries where data are consistent with vitamin B_{12} deficiency; this amount was considered sufficient since, unlike dietary sources of vitamin B_{12}, synthetic vitamin B_{12} is highly bioavailable.

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Interactions

Folate deficiency states may be produced by drugs such as antiepileptics, oral contraceptives, antituberculous drugs, alcohol, and folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim, and sulfonamides. In some instances, such as during methotrexate or antiepileptic therapy, replace-