Evidence-based Folic Acid Usage

Name(s): Folate, methylfolate, vitamins B8, B9 or B10.

Description: This is a water-soluble vitamin that functions as a coenzyme important for breaking down and utilising proteins. Folic acid is important for the formation of red blood cells. This is because folic acid is a carrier of carbon when forming haeme. Haeme is important for the formation of red blood cells because it is the iron-containing protein in haemoglobin.[1]

Absorption/Storage: Active transport (energy is required and this is the way most nutrients cross) and diffusion (movement from a greater concentration to a lesser concentration) are the two pathways folic acid is absorb by the gastrointestinal tract. The vascular system transports this vitamin where it is then stored in the liver.[1]

Recommended Dietary Allowance/Dietary Reference Intake:[2]

Persons	U.S. (mcg)
Birth to 3 years of age	65-150
4 to 8 years of age	200
9 to 13 years of age	300
Adolescent and adult males	400
Adolescent and adult females	400
Pregnant females	600
Breast-feeding females	500

Optimum Daily Allowance (Adult): 400-800 mcg.[3]

Tolerable Upper Intake Levels: [2]

Persons	U.S. (mcg)
Birth to 3 years of age	ND-300
4 to 8 years of age	400
9 to 13 years of age	600
Adolescent and adult males	800-1000
Adolescent and adult females	800-1000
Pregnant females	800-1000
Breast-feeding females	800-1000

Principal Uses: Birth defect prevention,[4-10] cervical dysplasia (abnormal pap smears) in women on oral contraceptives,[11-14] depression (especially in the elderly),[15-21] gingivitis (oral rinse only),[22-25] and high homocysteine (with vitamin B6 and B12 supplementation).[26-48]

Proposed Uses: Anaemia (for deficiency), atherosclerosis, breast cancer (reduces risk in women who consume alcohol), canker sores (for deficiency only), celiac disease (for deficiency only), colon cancer (prevention), heart attack, preeclampsia, sickle cell anaemia (for lowering homocysteine levels) and ulcerative colitis.[49]

Traditional Uses: Alzheimer's disease, anaemia (thalassemia, for deficiency), bipolar disorder/manic depression, Crohn's disease, dermatitis herpetiformis (for deficiency), diarrhoea, epilepsy, gingivitis (periodontal disease) (pill), gout, HIV support, lung cancer (reduces risk), osteoporosis, peripheral vascular disease, psoriasis, restless legs syndrome, seborrhoeic dermatitis, skin ulcers, stroke (for high homocysteine only) and vitiligo.[49]

Healthy Sources:
High (40%+ US RDA): Blackeye peas, brewer's yeast, kidney beans, rice germ, soy beans, soy flour, wheat bran and wheat germ.[50]

Medium (25-39% US RDA): asparagus, garbanzos, lentils, lima beans, mung beans and navy beans.[50]

Contraindications: In deciding to use folic acid, the risks of taking it must be weighed against the good it will do. This is a decision you and your health care professional will make. For folic acid, the following should be considered:

Allergies--Tell your health care professional if you have ever had any unusual or allergic reaction to folic acid. Also tell your health care professional if you are allergic to any other substances, such as foods, preservatives, or dyes.

Pregnancy--It is especially important that you are receiving enough vitamins when you become pregnant and that you continue to receive the right amount of vitamins, especially folic acid, throughout your pregnancy. The healthy growth and development of the foetus depend on a steady supply of nutrients from the mother. However, taking large amounts of a dietary supplement in pregnancy may be harmful to the mother and/or foetus and should be avoided.

Your health care professional may recommend that you take folic acid alone or as part of a multivitamin supplement before you become pregnant and during early pregnancy. Folic acid may reduce the chances of your baby being born with a certain type of birth defect (neural tube defects).

Breast-feeding--It is especially important that you receive the right amounts of vitamins so that your baby will also get the vitamins needed to grow properly. However, taking large amounts of a dietary supplement while breast-feeding may be harmful to the mother and/or baby and should be avoided.

Children--Problems in children have not been reported with intake of normal daily-recommended amounts.

Older adults--Problems in older adults have not been reported with intake of normal daily-recommended amounts.

Medicines or other dietary supplements--Although certain medicines or dietary supplements should not be used together at all, in other cases they may be used together even if an interaction might occur. In these cases, your health care professional may want to change the dose, or other precautions may be necessary. Tell your health care professional if you are taking any other dietary supplement or any prescription or non-prescription (over-the-counter [OTC]) medicine.

Other medical problems--The presence of other medical problems may affect the use of folic acid. Make sure you tell your health care professional if you have any other medical problems, especially:

- Pernicious anaemia (a type of blood problem)--Taking folic acid while you have pernicious anaemia may cause serious side effects. You should be sure that you do not have pernicious anaemia before beginning folic acid supplementation.[51]

Interactions:

Decreases Vitamin Availability:	Erythromycin, isoniazid, lansoprazole, loop diuretics, metformin, neomycin, nitrous oxide, spironolactone, sulfamethoxazole, tetracycline, thiazide diuretics,[49] aminopterin, antacids, anticonvulsants, aspirin, bile acid sequestrants, histamine blockers, NSAIDS, methotrexate, oral contraceptives, triamterene, trimethoprim,[49,52] antiprotozoal drugs, bicarbonates, charcoal, chloramphenicol, cholesterol lowering drugs, corticosteroids, fibre supplements, nitrofurantoin, nitrofurazone, oestrogens, pancreatic enzymes, para-aminosalicylic acid, phenylbutazone, sulfasalazine, triazinate,[52] barbiturates, ethanol, glutethamide,[53] and chloramphenicol.[52,54]
Increases Vitamin Availability:	SAMe, vitamin B6, choline,[49] vitamin B12 and zidovudine.[52]
Is Decreased By Vitamin Availability:	Methotrexate,[49] zinc,[52] fenofibrate side effects and antiepileptics.[54,55]
Is Increased By Vitamin Availability:	Fluoxetine and lithium.[49]

Deficiency: Megablastic anaemia is a condition caused by a deficiency in folate. In this form of anaemia, the red blood cells are too large. Since the RBC's are too large there are not enough of them. Just because the cells are larger that does not mean they carry more oxygen, in fact, they carry the same amount as the normal size red blood cells. Anaemia may be spotted by sleeplessness and depression. The results of folate deficiency include tongue inflammation, diarrhoea, lesions, and poor growth. Mental disorders may also result such as forgetfulness, and neurological irritability. Pregnant women often experience a deficiency in folate because the foetus is rapidly growing, pulling from the mother. If the foetus does not get enough folate it may result in cleft palate, brain damage, and spina bifida.[1]

Toxicity/Side Effects: Along with its needed effects, a

dietary supplement may cause some unwanted effects. Although folic acid does not usually cause any side effects, check with your health care professional as soon as possible if any of the following side effects occur:

Rare

- Fever; general weakness or discomfort; reddened skin; shortness of breath; skin rash or itching; tightness in chest; troubled breathing; wheezing

Other side effects not listed above may also occur in some individuals. If you notice any other effects, check with your health care professional.[51]

Treatment For Overdose: None.

Storage: To store this dietary supplement:

- Keep out of the reach of children.
- Store away from heat and direct light.
- Do not store in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the dietary supplement to break down.
- Do not keep outdated dietary supplements or those no longer needed. Be sure that any discarded dietary supplement is out of the reach of children.[51]

References:

1. Dr. Morrow's Library of Vitamins, Minerals, Amino Acids, and Herbs: Inositol. [Online] http://www.nutritiondynamics.com/cgi-bin/process.asp?product=Folic+Acid
2. National Academy of Sciences Food and Nutrition Board. (2000). Dietary reference intakes: Applications in dietary assessment. Washington, DC: National Academy Press.
3. Balch, P.A. & Balch, J.F. (2000). Prescription for nutritional healing (third edition). Garden City Park: Avery Publishing.
4. Werler, M.M., Shapiro, S. & Mitchell, A.A. (1993). Periconceptional folic acid exposure and risk of occurrent neural tube defects. JAMA, 269: 1257-1261.
5. Milunsky, A. et al. (1989). Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. JAMA, 262: 2847-2852.
6. Hibbard, E.D. & Smithells, R.W. (1965). Folic acid metabolism and human embryopathy. Lancet, i: 1254.
7. Smithells, R.W., Sheppard, S. & Schorah, C.J. (1976). Vitamin deficiencies and neural tube defects. Archives of Diseases in Children, 51: 944-950.
8. Laurence, K.M., et al. (1981). Double blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural tube defects. British Medical Journal, 282: 1509-1511.
9. Smithells, R.W., et al. (1983). Further experience of vitamin supplementation for the prevention of neural tube defects. Lancet, I: 1027-1033.
10. [No authors listed]. (2000). Multicentric study of efficacy of periconceptional folic acid containing vitamin supplementation in prevention of open neural tube defects from India. Indian Journal of Medical Research, 112:206-11.
11. Streiff, R. (1970). Folate deficiency and oral contraceptives. JAMA, 214: 105-108.
12. Whitehead, N., Reyner, F. & Lindenbaum, J. (1973). Megaloblastic changes in the cervical epithelium associated with oral contraceptive therapy and reversal with folic acid. JAMA, 226: 1421-1424.
13. Butterworth, C., Hatch, K., Gore, H., et al. (1982). Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. American Journal of Clinical Nutrition, 35: 73-82.
14. Butterworth, C.E., Jr., Hatch, K.D., Macaluso, M., et al. (1992). Folate deficiency and cervical dysplasia. JAMA, 267:528–533.
15. Crellin, R. Bottiglieri, T. & Reynolds, E.H. (1993). Folates and psychiatric disorders. Clinical potential. Drugs, 45: 623-636.
16. Godfrey, P.S.A., et al. (1990). Enhancement of recovery from psychiatric illness by methyl folate. Lancet, 336: 392-395.
17. Thornton, W.E. & Thornton, B.P. (1977). Geriatric mental function and folic acid, a review and survey. Southern medical Journal, 70: 919-922.
18. Wesson, V.A., et al. (1994). Change in folate status with antidepressant treatment. Psychiatry Research, 53: 313-322.
19. Zucker, D., et al. (1981). B12 deficiency and psychiatric disorders: A case report and literature review. Biological Psychiatry, 16: 197-205.
20. Kivela, S.L., Pahkala, K. & Eronrn, A. (1989). Depression in the aged: Relation to folate and vitamins C and B12. Biological Psychiatry, 26: 209-213.
21. Coppen, A. & Bailey, J. (2000). Enhancement of the antidepressant action of fluoxetine by folic acid: a

randomised, placebo-controlled trial. Journal of Affective Disorders, 60(2): 121-130.
22. Pack, A.R. (1984). Folate mouthwash: effects on established gingivitis in periodontal patients. Journal of Clinical Periodontology, 11(9): 619-628.
23. Thomson, M.E. & Pack, A.R. (1982). Effects of extended systemic and topical folate supplementation on gingivitis of pregnancy. Journal of Clinical Periodontology, 9(3): 275-280.
24. Pack, A.R. & Thomson, M.E. (1980). Effects of topical and systemic folic acid supplementation on gingivitis in pregnancy. Journal of Clinical Periodontology, 7(5): 402-414.
25. Vogel, R.I., Fink, R.A., Frank, O. & Baker, H. (1978). The effect of topical application of folic acid on gingival health. Journal of Oral Medicine, 33(1): 20–22.
26. Landgren, F., et al. (1995). Plasma homocysteine in acute myocardial infarction: Homocysteine-lowering effect of folic acid. Journal of Internal Medicine, 237: 381-388.
27. Ubbink, J.B., et al. (1993). Vitamin b12, vitamin b6 and folate nutritional status in men with hyperhomocysteinemia. American Journal of Clinical Nutrition, 57: 47-53.
28. Ubbink, J.B. van der Merwe, W.J. & Delport, R. (1993). Hyperhomocysteinemia and the response to vitamin supplementation. Clinical Investigation, 71: 993-998.
29. Abdelfatah, A., Ducloux, D., Toubin, G., Motte, G., Alber, D. & Chalopin, J.M. (2002). Treatment of hyperhomocysteinaemia with folic acid reduces oxidative stress in renal transplant recipients. Transplantation, 73(4): 663-665.
30. Rydlewicz, A., Simpson, J.A., Taylor, R.J., Bond, C.M. & Golden, M.H. (2002). The effect of folic acid supplementation on plasma homocysteine in an elderly population. QJM, 95(1): 27-35.
31. Fohr, I.P., Prinz-Langenohl, R., Bronstrup, A., Bohlmann, A.M., Nau, H., Berthold, H.K. & Pietrzik, K. (2002). 5,10-Methylenetetrahydrofolate reductase genotype determines the plasma homocysteine-lowering effect of supplementation with 5-methyltetrahydrofolate or folic acid in healthy young women. American Journal of Clinical Nutrition, 75(2): 275-282.
32. Quinlivan, E.P., McPartlin, J., McNulty, H., Ward, M., Strain, J.J., Weir, D.G. & Scott, J.M. (2002). Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. Lancet, 19;359(9302):227-228.
33. Pullin, C.H., Ashfield-Watt, P.A., Burr, M.L., Clark, Z.E., Lewis, M.J., Moat, S.J., Newcombe, R.G., Powers, H.J., Whiting, J.M. & McDowell, I.F. (2001). Optimisation of dietary folate or low-dose folic acid supplements lower homocysteine but do not enhance endothelial function in healthy adults, irrespective of the methylenetetrahydrofolate reductase (C677T) genotype. Journal of the American College of Cardiology, 38(7): 1799-1805.
34. De Vecchi, A.F., Patrosso, C., Novembrino, C., Finazzi, S., Colucci, P., De Franceschi, M, Fasano, M.A. & Bamonti-Catena, F. (2001). Folate supplementation in peritoneal dialysis patients with normal erythrocyte folate: effect on plasma homocysteine. Nephron, 89(3): 297-302.
35. Brouwer, I.A., van Dusseldorp, M., Thomas, C.M., van der Put, N.M., Gaytant, M.A., Eskes, T.K., Hautvast, J.G. & Steegers-Theunissen, R.P. (2000). Homocysteine metabolism and effects of folic acid supplementation in patients affected with spina bifida. Neuropaediatrics, 31(6):298-302.
36. Henning, B.F., Zidek, W., Riezler, R., Graefe, U., Tepel, M. (2001). Homocyst(e)ine metabolism in haemodialysis patients treated with vitamins B6, B12 and folate. Research in Experimental Medicine (Berl). 200(3): 155-168.
37. Thambyrajah, .J, Landray, M.J., Jones, H.J., McGlynn, F.J., Wheeler, D.C. &Townend, J.N. (2001). A randomised double-blind placebo-controlled trial of the effect of homocysteine-lowering therapy with folic acid on endothelial function in patients with coronary artery disease. Journal of the American College of Cardiology, 37(7): 1858-1863.
38. Brouwer, I.A., van Dusseldorp, M., Thomas, C.M.G., Duran, M., Hautvast, J.G.A.J., Eskes, T.K.A.B. & Steegers-Theunissen, R.P. (2000). Low-Dose folic acid supplementation decreases plasma homocysteine concentrations: a randomised trial. Indian Heart Journal, 52(7 Suppl): S53-58.
39. Dierkes, J., Domrose, U., Bosselmann, K.P., Neumann, K.H. & Luley C. (2001). Homocysteine lowering effect of different multivitamin preparations in patients with end-stage renal disease. Journal of Renal Nutrition, 11(2):67-72.
40. Hauser, A.C., Hagen, W., Rehak, P.H., Buchmayer, H.,

Fodinger, M., Papagiannopoulos, M., Bieglmayer, C., Apsner, R., Koller, E., Ignatescu, M., Horl, W.H. & Sunder-Plassmann, G. (2001). Efficacy of folinic versus folic acid for the correction of hyperhomocysteinaemia in haemodialysis patients. American Journal of Kidney Disease, 37(4):758-765.
41. Wald, D.S., Bishop, L., Wald, N.J., Law, M., Hennessy, E., Weir, D., McPartlin, J. & Scott, J. (2001). Randomised trial of folic acid supplementation and serum homocysteine levels. Archives of Internal Medicine, 161(5): 695-700.
42. Manns, B., Hyndman, E., Burgess, E., Parsons, H., Schaefer, J., Snyder, F. & Scott-Douglas, N. (2001). Oral vitamin B(12) and high-dose folic acid in haemodialysis patients with hyper-homocyst(e)inemia. Kidney International, 59(3): 1103-1009.
43. Bostom, A.G., Shemin, D., Gohh, R.Y., Beaulieu, A.J., Bagley, P., Massy, Z.A., Jacques, P.F., Dworkin, L. & Selhub, J. (2001). Treatment of hyperhomocysteinaemia in haemodialysis patients and renal transplant recipients. Kidney International Supplement, 78:S246-252.
44. Murua, A.L., Quintana, I., Janson, J., Batista, M., Camera, M.I. & Kordich, L.C. (2000). Plasmatic homocysteine response to vitamin supplementation in elderly people. Thrombosis Research, 100(6): 495-500.
45. Yango, A., Shemin, D., Hsu, N., Jacques, P.F., Dworkin, L., Selhub, J. & Bostom, A.G. (2001). Rapid communication: L-folinic acid versus folic acid for the treatment of hyperhomocysteinaemia in haemodialysis patients. Kidney International, 59(1): 324-327.
46. McKay, D.L., Perrone, G., Rasmussen, H., Dallal, G. & Blumberg, J.B. (2000). Multivitamin/mineral supplementation improves plasma B-vitamin status and homocysteine concentration in healthy older adults consuming a folate-fortified diet. Journal of Nutrition, 130(12): 3090-3096.
47. MacMahon, M., Kirkpatrick, C., Cummings, C.E., Clayton, A., Robinson, P.J., Tomiak, R.H., Liu, M., Kush. D. & Tobert, J. (2000). A pilot study with simvastatin and folic acid/vitamin B12 in preparation for the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). Nutrition, Metabolism and Cardiovascular Disease,10(4): 195-203.
48. Chambers, J.C., Ueland, P.M., Obeid, O.A., Wrigley, J., Refsum, H., Kooner, J.S. (2000). Improved vascular endothelial function after oral B vitamins: An effect mediated through reduced concentrations of free plasma homocysteine. Circulation, 102(20): 2479-2483.
49. Austin, S., Gaby, A., Appleton, J. et al. (2001). HealthNotes Online. [Online] http://healthnotes.com
50. Murray, M.T. (1996). Encyclopaedia of nutritional supplements. Rocklin, CA: Prima.
51. National Library of Medicine. (1999). Folic Acid - Vitamin B9 (systemic). [Online] http://www.nlm.nih.gov/medlineplus/druginfo/folicacidvitaminb9systemic202250.html
52. Meletis, C. & Jacobs, T. (1999). Interactions between drugs & natural medicines. Sandy, OR.: Eclectic Medical Publications.
53. Gillis, C. (editor). (1999). Compendium of pharmaceuticals and specialties. Ottawa, Canada: Canadian Pharmacists Association.
54. American Society of Health-System Pharmacists. (2000). AHFS drug information. Bethesda, MD: American Society of Health-System Pharmacists.
55. Facts and Comparisons. (1997). Drug facts and comparisons, 1998 edition. St. Louis, Missouri: Facts and Comparisons.

Compiled by:
Michael John Nisbett, HBScN, RN
MSc (Nutrition) Candidate