ERNA

folate

FACT SHEET

Folate is a generic term for food folates (polyglutamate derivates) and folic acid. Folate plays an important role in several physiological functions including normal cell division, especially for cell systems with a high cell division rate (e.g. blood cells, mucosa of the gut)

Importance for health

Neural tube defects

Neural tube defects (NTD) are one of the most significant congenital causes of morbidity and mortality in infants, effecting in excess of 250,000 newborns every year worldwide. An intake of 400 µg per day of folic acid has been demonstrated to dramatically reduce the prevalence of NTD effect.[1] In Europe, more than 90% of women of childbearing age have intakes below this optimal level.[2] One strategy is to increase supplementation among the target population, although this depends on ensuring that the women receive folic acid prior to pregnancy, given that the neural tube often closes before women know they are pregnant. Public understanding of this problem in Europe is generally still poor, although campaigns have noted some success (see page 2). The US authorities have implemented a policy to fortify flour with folic acid. Findings have suggested a reduction in NTDs of between 20% and 50% since fortification begun.

Hearty health and homocysteine

The level of homocysteine is normally rigorously controlled within a narrow range in both human cells and circulating plasma. Even moderate elevation of homocysteine has been shown in numerous studies to be a risk factor for heart attacks and strokes.[3] A recent meta-analysis concluded that after adjustment for known cardiovascular risk factors a 25% reduction in plasma homocysteine is associated with a reduction in risk for ischemic heart disease of 11% and of stroke of 19%.[4] There has consequently been a lot of interest in determining in how to decrease homocysteine plasma levels.

The level of homocysteine is controlled by the activity of three enzymes, each of which requires one or more vitamins for their activity.[5] These are cystathionine synthase (vitamin B_6), methionine synthase (vitamin B_{12}) together with methylenetetrahydrofolate reductase (MTHFR, folate and vitamin B_2). In all populations a common genetic variant (also called genetic polymorphism) exists of MTHFR. The consequence of polymorphism is a reduced activity of the enzyme in about 10% of the population and a significant but less dramatic reduction in about half of the population.[6]

As mentioned earlier, MTHFR uses riboflavin (vitamin B_2) as a cofactor. The reduced activity of the genetic variant CÆT 677 is due to loss of this cofactor. In a very important study, it has been shown that the reduced acitivity of this enzyme and consequently the resultant elevation of homocysteine is absolutely dependent upon the riboflavin status.[7] Further, in a recent human intervention study riboflavin normalised the activity of this enzyme in those with the common genetic defect giving them optimal homocysteine levels.[8]

Without an extensive laboratory investigation, most people don't know which of the nutrients they need and it seems prudent to take supplements containing folic acid together with the vitamins B_2, B_6 and B_{12} to be sure of having optimum homocysteine levels.

1 Scott JM, Weir DG, Molloy A, 0cPartlin J, Daly L, Kirke P. Folic acid metabolism and mechanisms of neural tube defects. In: Bock G, Marsh J, eds. Ciba Foundation Symposium 181, Neural Tube Defects. Chichester: John Wiley and Sons, 1994:180-91.

2 EC Scientific Committee on Food, Opinion of Scientific Committee on Food on the tolerable upper intake level of folate, European Commission 28.11.2000.

3 Wald NJ, Watt HC, Law MR, Weir DG, McPartlin J, Scott JM "Homocysteine and ischaemic heart disease: results of a prospective study with implications on prevention" Archives of Internal Medicine (1998) 158, 862-867.

4 Klerk M, Verhoef P, Clarke R, Blom H, Kok F, Schaten E MTHFR 677 CÆT Polymorphism and risk of coronary heart disease. Journal of the American Medical Association (2002) 288, 2023-2031.

5 Scott JM, Weir DG Folic acid, homocysteine and one carbon metabolism: a review of the essential biochemistry. Journal of Cardiovascular Risk (1998) 5, 223-227.

6 Bailey LB, Gregory JF Polymorphisms of methylenetetrahydrofolate reductase and other enzymes: metabolic significance, risks and impact on folate requirement. Journal of Nutrition (1999) 129, 919-922.

7 McNulty H, McKinley MC, Wilson B, McPartlin J, Strain JJ, Weir DG, Scott JM Impaired functioning of thermolabile methylenetetrahydrofolate reductase is dependent on riboflavin status: implications for riboflavin requirements. American Journal of Clinical Nutrition (2002) 76, 436-441.

Dietary sources

The consumption of folate must be regular, as human beings are unable to synthesise folate. Green vegetables provide one of the most important sources of folate. Spinach, salad, asparagus, tomatoes, cucumbers, whole-grain products, liver and some tropical fruits are also rich in folate. Only trace amounts are found in meat and fish. (See Table 1)

Table 1: Folate content in food[9]

Food	Dietary folate equivalent (µg/100 g)
Spinach	56
White cabbage	36
Broccoli	25
Salad	23
Tomatoes	20
Wholemeal flour	38
Orange	31
Orange juice	16
Avocado	30
Banana	16
Cheese	19-42
Milk	4
Egg	27
Chicken	5
Beef	3
Liver	242
Salmon	5

European folate intake

In most European countries, current average folate intake does not meet current national recommendations. The mean dietary folate intake of adults is 291 µg/d for men and 247 µg/d for women. The highest folate intake was reported in the Parisian area of France, whilst the lowest folate intakes were found in Swedish and Dutch populations. These differences in folate intake partly reflect traditional dietary habits among Europe. A Mediterranean diet consisting of higher portions of vegetables, fruits and whole grains may help explain higher intakes of folate in France, Spain and Portugal.[10]

In spite of specific national recommendations (see below) for this population group, women of a childbearing age in particular do not consume enough folate. In Europe, more than 90% of women of a childbearing age are estimated to have intake below this optimal level.[2] An increase in average daily folate intake has been seen (of 47 µg for men and 73 µg for women) between 1987 and 2001, but not sufficiently to meet recommendations of 400 µg/day.

Table 2: Mean adult* folate intake in EU countries (µg/day)[2, 7, 11]

	Mean intake of folate (µg/d)	
Country	Male	Female
Germany	236	211
Netherlands	215	173
Spain	317	303
Portugal	300	265
UK	311	213
Denmark	304	249
Sweden	230	194
Ireland	332	260

* Generally data for persons aged between 16 and 64, although this varies slightly from country to country.

8 McNulty H, Dowey LC, Scott JM, Molloy AM, McArena LB, Hughes JP, Ward, M, Strain JJ, Riboflavin supplementation lowers plasma homocysteine in individuals homozygous for the MTHFR C677T polymorphism. Journal of Inherited Metabolic Disease (2003) 26, Suppl. 1, 12.

9 Bundesgesundheitsamt, Bundeslebensmittelschlüssel für Verzehrserhebungen (BLS) Version II 1999

10 De Bree A et al., Folate intake in Europe: recommended, actual and desired intake, European Journal of Clinical Nutrition 51 (1997) 643-660.

11 Deutsche Gesellschaft für Ernährung (DGE), Ernährungsbericht 2000, DGE, Frankfurt (2000) 46-57, Konings E JM et al., Folate intake of the Dutch population according to newly established liquid chromatography data for foods, Am J Clin Nutr 73 (2001) 765-776., O'Brien M M et al., The North/South Ireland Food Consumption Survey: vitamin intakes in 18-64-year-old adults, Public Health Nutrition 4/5a (2001) 1069-1079.

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Recommended intakes

The Recommended Dietary Allowances (RDA) is a general term to describe the intake levels estimated to be sufficient to cover the needs of the majority of the healthy population. The variation in recommended intake levels is due to the fact that each country has its own approach, correction factors and publications on which the recommendations are based. The recommended intakes vary between 200-400 µg/day. Specific recommendations are often set for women of childbearing age. For example, in Austria, Belgium, Germany, Netherlands and the UK, it is recommended that women take a supplement of 400 µg/day from at least 4 weeks prior to conception until at least 8-12 weeks of pregnancy.

Country	Sub-group	RDA (µg/d)
France	Adults 18+	200
Germany/	Children 7-10	300
Austria/	Adults 10+	400
Switzerland	Pregnant women	600
UK	Children 7-10	150
	Adults 11+	200
	Pregnant women	300
	Lactating women	260
Netherlands	Adults	200
	Pregnant women	400
Belgium	Adults	200
	Pregnant women	400
	Lactating women	350
Denmark	Adults	200
Sweden	Adults	300
EU Reference Labelling Value	Adults	400

Table 3: Recommended Dietary Allowances for folate in Europe

Consumer understanding of folate

Only 1 in 3 European consumers know of the relationship between folic acid intake and prevention neural tube defects.[13] Following an extensive campaign to improve public understanding of this relationship by UK authorities, awareness of the importance of folic acid in the UK among the target group increased from 9% in 1995 to 49% in 1999.[14] The impact of this initiative is also clear in a survey of the general population undertaken in 1999: when asked which vitamin is most associated with the prevention of birth defects, 24 % of UK respondents answered correctly, compared to 5% in Spain, 2% in Germany and Spain and 0% in France.[15]

Stability[16]

Naturally occuring food folate is rather unstable under exposure to oxygen, light and higher temperatures. Peas and spinach, for example, stored for 5 days, will lose around 50% of their folate content.[17] Substantial losses of folate also occur due to food processing or cooking.

Food supplements

Despite the recommendations of relatively high folate intake, consumption of food supplements containing folic acid remains low. In Ireland, food supplements provide on average 2.4% of total folate intake for men and 6.4% for women.[18] However, in the Netherlands, where only 1,7% of the study population took folic acid supplements[13], supplements provided approximately 50% of mean total folate intake.[8] The German Nutrition Survey of 1998 provides data on nutrient intake as consumed from usual diet and additionally from vitamin and mineral supplements. This study has demonstrated that approximately 90% of men and almost 100% of women do not reach the reference value of 400 µg/d dietary folate equivalent solely through the diet. The German recommendations for folate intake can only be reached, if the normal diet is

12 EC Scientific Committee on Food: Opinion of the Scientific Committee on Food on the revision of reference values for nutrition labelling. European Commission. (2003).

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14 COMA, Department of Health. Report on Health and Social Subjects. Folic acid and the Prevention of Disease. The Stationery Office. London. (2000).

15 Gallup European Consumers Awareness and Behaviour Survey on Vitamin and Mineral Supplements and Fortified Foods (Roche Vitamins Europe, 1999).

16 See Elmadfa I, Fritzsche D, Die große GU Vitamin und Mineralstoff Tabelle. Gräfe und Unzer Verlag, München (1998) 21 and Hawkes J.G., Villota R., Folates in foods: Reactivity, stability during processing, and nutritional implications, Critical Reviews in Food Science and Nutrition Vol 28 Issue 6 (1989) 439-538.

17 Ros G, Variety, Ripening and Processing Effects on Folates in Vegetables, Folate Func Health, Issue 4, (2002).

18 Irish Universities Nutrition Alliance (IUNA), The North-South Ireland Food Consumption Survey (2001).

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Food Supplements continued

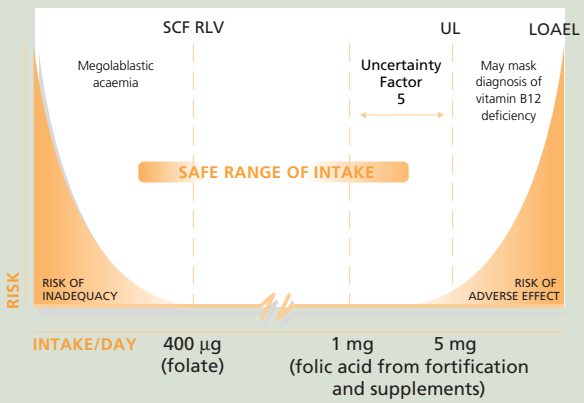
supplemented.[19] The greatest recorded intake from food supplements is among UK women aged over 50 years with the highest intake of total folate (97.5 percentile) who consumed a daily average intake of 90 µg.[20] Table 4 provides a review of the range of folic acid content in food supplements currently sold freely in the EU, i.e. those that the consumer can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines). Food supplements sold in pharmacies and subject to specific controls are not included.

Country	Content (µg/day)
Denmark	100-400
Germany	100-900
Ireland	100-400
Netherlands	100-1000
Portugal	100-400
Sweden	100-400
UK	100-800

Table 4: Range of folic acid in food supplements freely sold in EU markets[21]

Safety

The EC Scientific Committee on Food (SCF) and the US Food and Nutrition Board (FNB) made a detailed risk assessment of folate and opinions largely converged. There is no adverse effect of folate from the diet. Excessive folic acid intake could mask vitamin B_{12} deficiency anaemia. Only 8 cases of adverse effects were reported at doses lower than 5 mg/d. A relatively large uncertainty factor of 5 was applied to this LOAEL (Lowest Observed Adeverse Effect Level). The Tolerable Upper Intake Level was therefore established at 1 mg/day by the SCF to include dietary intake and intake from food supplements and fortified foods.[2] The FNB established a UL of 1 mg/day for intake of fortified foods and food supplements. It is unlikely that daily intake of folic acid from supplementation would regularly exceed 1 mg. Those at risk in relation to excessive intake of folic acid are those with a marginal intake of vitamin B_{12}, namely groups avoiding animal products, such as vegans.[22]



Fortified foods

Fortification of foods is currently not generally allowed in many EU Member States (e.g. Scandinavia, France, Greece), or limited to certain dietetic foods (Austria).[23] In some European countries special product categories such as breakfast cereals may be fortified with folic acid. In the UK, many cereals and breads are fortified with folic acid, providing 25-100 µg per serving. Exceptionally in the EU, the German market contains a wide range of food fortified with folic acid (see Table 5) A primary prevention strategy of fortifying flour with folic acid as undertaken in the US, Canada, Australia and South Africa has not been implemented in the EU.[24]

Food	µg folic acid/100g
Salt	10 000
Breakfast Cereals	165-340
Sweets	30-800
Convenience food (soup)	182-200
Beverages	30-100
Dairy products	3-40
Cocoa	200

Table 5: Examples of fortified foods on the German market[25]

19 Beitz R et al. Vitamins – dietary intake and intake from dietary supplements in Germany, European Journal of Clinical Nutrition 56 (2002) 539-545.

20 UK Office for National Statistics, The National Diet & Nutrition Survey (NDNS): adults aged 19 to 64 years (2003).

21 Market survey undertaken by the European Responsible Nutrition Alliance in 2001-2003.

22 Institute of Medicine Food and Nutrition Board. Folate. In: Dietary Reference Intakes for Thiamin, Vitamin B12, Pantothenic Acid, Biotin and Chlorine, National Academy Press, Washington (2000) 196-306.

23 European Advisory Service, Marketing Food Supplements, fortified foods and functional foods in Europe : Legislation & Practice (2002).

24 Grünewald-Funk D, Internationaler Stand der Folsäuresupplementation Akt. Ernähr.-Med. 24 (1999) A50-A51.

25 Survey of German market undertaken in September 2002.