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Nutrient Reference Values for Australia and New Zealand
Including Recommended Dietary Intakes

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FOLATE

BACKGROUND

Folate is the commonly used group name for folic acid (pteroyl glutamic acid, or PGA) and its derivatives with similar activity. In foods and in the body folates are usually in the reduced form (tetrahydrofolate, or THF) and conjugated with up to seven glutamate residues and one of several types of one-carbon groups. PGA is used in supplements and for food fortification as it is more stable than the other derivatives.

Folate functions as a coenzyme in single-carbon transfers in the metabolism of nucleotides and amino acids. It is essential for the formation of thymidylate (TMP) for DNA synthesis, so that without folate, living cells cannot divide. The need for folate is higher when cell turnover is increased, such as in fetal development. It is also involved in purine synthesis, in the generation of formate and in amino acid interconversions. Homocysteine is methylated by methyl-THF to produce methionine, which is in turn used for the synthesis of *S*-adenosyl-methionine an important methylating agent *in vivo* (Wagner 1996).

Food folates are hydrolysed to monoglutamate forms in the gut to allow their absorption across the intestine. The monoglutamates enter the portal circulation and are metabolised to polyglutamate derivatives in the liver. They are either retained, or released to the blood as reconverted monoglutamates or to bile. The liver contains about 50% of the body stores of folate.

Folate is a substrate and vitamin B_{12} is a coenzyme for the formation of MTHF that depends on the regeneration of THF, the parent compound in the homocysteine-to-methionine conversion. If either folate or vitamin B_{12} is deficient, megaloblastic changes occur in bone marrow and other replicating cells from lack of 5,10-MTHF for DNA synthesis.

The bulk of excretion products are folate cleavage products. Intact urinary folate accounts for only a small percentage of dietary folate. Biliary excretion of folate can be as high as 100 µg/day (Herbert & Das 1993, Whitehead 1986), however much of this is reabsorbed.

Folate is difficult to measure in foods because it is present in different forms, so food databases can be inaccurate. However, the main sources of folate in Australia and New Zealand according to the National Nutrition Surveys undertaken in 1995 and 1997, respectively (ABS 1998, MOH 1999), are cereals, cereal products and dishes based on cereals (about 27%) and vegetables and legumes (about 29%). Fruit provides about 8–10%. Orange juice is contributing a greater amount than in the past due to the recent introduction of fortification with folate.

Folate requirements can be affected by bioavailability, nutrient interactions, smoking, certain drugs and genetic variations. Notably, the C667T polymorphism that causes MTHF reductase deficiency is found in 2–16% of white populations (van der Put et al 1995). It is likely that individuals who are homozygous for this polymorphism may have a higher requirement for folate.

Bioavailability of folates in food is about 50–60% whereas that of the folic acid used to fortify foods or as a supplement is about 85% (Sauberlich et al 1987, Gregory 1989, 1995, 1997, Pfeiffer et al 1997, Cuskelly et al 1996). Folic acid as a supplement is almost 100% bioavailable on an empty stomach. Picciano et al (2004) have recently demonstrated that the inclusion of cows' milk in the diet enhances the bioavailability of food folate as assessed by changes in erythrocyte folate and plasma total homocysteine concentrations, but not when assessed by plasma folate concentrations. Some controlled studies to assess requirements have used a defined diet containing food folate and supplemented with folic acid, so the term dietary folate equivalents (DFE) has been used to accommodate the varying bioavailabilities.

1 µg dietary folate equivalent (DFE)	= 1 µg food folate
	= 0.5 µg folic acid on an empty stomach
	= 0.6 µg folic acid with meals or as fortified foods

Inadequate folate intake leads to decreased serum folate, then decreased erythrocyte folate, a rise in homocysteine and megaloblastic changes in bone marrow and other rapidly dividing tissues (Eichner & Hillman 1971). As depletion progresses, macrocytic cells are produced and macrocytic anaemia develops. Eventually, full-blown anaemia results in weakness, fatigue, irritability and palpitations. Folic acid supplementation in pregnancy can reduce both the occurrence and recurrence of neural tube defects in the newborn (Bower & Stanley 1989, CDC 1992, Czeizel & Dudas 1992, Kirke et al 1993, Laurence et al 1981, Wald et al 1991).

Indicators of folate requirement include erythrocyte, serum or urinary folate, plasma homocysteine and haematological status measures as well as clinical endpoints such as neural tube defects or chronic degenerative disease. Of these, erythrocyte folate is generally regarded as the primary indicator as it reflects tissue folate stores. For some age groups, erythrocyte folate is used in conjunction with plasma homocysteine and plasma or serum folate.

RECOMMENDATIONS BY LIFE STAGE AND GENDER

Infants	**AI**	**Folate (as dietary folate equivalents)**
0–6 months	**65 µg/day (as folate)**	
7–12 months	**80 µg/day**	

***Rationale*:** The AI for 0–6 months was calculated by multiplying together the average intake of breast milk (0.78 L/day) and the average concentration of folate in breast milk of 85 µg/L (Asfour et al 1977, Ek & Magnus 1982, FNB:IOM 1998, Salmenpera et al 1986, Smith et al 1983, 1985), and rounding.

The AI for 7–12 months was set by the reference body weight ratio, estimating up from young infants or down from adults. Both estimates gave an AI of 80 µg/L which is also consistent with data for older, fully breast-fed or fully formula-fed infants in the studies of Asfour et al (1977), Ek & Magnus (1982), Salmenpera et al (1986) and Smith et al (1983).

Children & adolescents	**EAR**	**RDI**	**Folate (as dietary folate equivalents)**
All			
1–3 yr	**120 µg/day**	**150 µg/day**	
4–8 yr	**160 µg/day**	**200 µg/day**	
Boys			
9–13 yr	**250 µg/day**	**300 µg/day**	
14–18 yr	**330 µg/day**	**400 µg/day**	
Girls			
9–13 yr	**250 µg/day**	**300 µg/day**	
14–18 yr	**330 µg/day**	**400 µg/day**	

***Rationale*:** As there are no experimental data for children, the EARs were set by extrapolation from adult data using metabolic body weight ratios with an allowance for growth as per FNB:IOM (1998). In the absence of information on the standard deviation of the requirement, the RDI was set assuming a CV of 10% for the EAR.

Adults	**EAR**	**RDI**	**Folate (as dietary folate equivalents)**
Men			
19–30 yr	**320 µg/day**	**400 µg/day**	
31–50 yr	**320 µg/day**	**400 µg/day**	
51–70 yr	**320 µg/day**	**400 µg/day**	
>70 yr	**320 µg/day**	**400 µg/day**	
Women			
19–30 yr	**320 µg/day**	**400 µg/day**	
31–50 yr	**320 µg/day**	**400 µg/day**	
51–70 yr	**320 µg/day**	**400 µg/day**	
>70 yr	**320 µg/day**	**400 µg/day**	

***Rationale*:** The EAR for younger adults was set by reference to metabolic balance studies, notably the long term maintenance study in women that found no difference in mean final erythrocyte folate at 400 µg/day compared to 200–300 µg/day but a higher number of subjects with low erythrocyte folate, lower mean plasma folate and increased homocysteine levels (O'Keefe et al 1995). Other studies taken into account as cited in FNB:IOM (1998) were Herbert (1962a,b), Jacob et al (1994), Krumdieck et al (1978), Milne et al (1983), Sauberlich et al (1987), Stites et al (1997), von der Porten (1992) and Zalusky & Herbert (1961). For adults over 51 years, the requirements were based on metabolic, observational and epidemiological studies (Bates et al 1980, Garry et al 1982, Jagerstad 1977, Jagerstad & Westesson 1979, Koehler et al 1996, Ortega et al 1993, Rosenburg 1992, Sayoun 1992, Sayoun et al 1988, Selhub et al 1993, Tucker et al 1996, 1984).

In the absence of information on the SD of the requirement, the RDI was set assuming a CV of 10% for the EAR.

***Special note*:** Evidence about the levels of folic acid needed in women to prevent neural tube defects did not form the basis for the adult EARs and RDIs. Women capable of, or planning, pregnancies should consume additional folic acid as a supplement or in the form of fortified foods at a level of 400 µg/day folic acid for at least one month before and three months after conception, in addition to consuming food folate from a varied diet.

Pregnancy	**EAR**	**RDI**	**Folate (as dietary folate equivalents)**
14–18 yr	**520 µg/day**	**600 µg/day**	
19–30 yr	**520 µg/day**	**600 µg/day**	
31–50 yr	**520 µg/day**	**600 µg/day**	

***Rationale*:** Folate requirements increase substantially in pregnancy. This recommendation does not include consideration of additional needs to prevent neural tube defects as the neural tube is formed before most women know they are pregnant. The data indicate that maximal protection against NTD is obtained when the mother is consuming very high levels (5,000 µg) of folic acid as supplements, in the

month preceding conception and in the first trimester (Wald et al 2001). Recommendations are based on evidence from controlled metabolic studies (Caudill et al 1997) and a series of population studies (Chanarin et al 1968, Colman et al 1975, Dawson 1966, Hansen & Rybo 1967, Lowenstein et al 1966, Qvist et al 1986, Willoughby 1967, Willoughby & Jewel 1966). The RDI was estimated assuming a CV of 10% for the EAR.

Lactation	**EAR**	**RDI**	**Folate (as dietary folate equivalents)**
14–18 yr	**450 µg/day**	**500 µg/day**	
19–30 yr	**450 µg/day**	**500 µg/day**	
31–50 yr	**450 µg/day**	**500 µg/day**	

***Rationale*:** To estimate total folate requirement for lactation, the amount needed to provide sufficient breast milk folate (including a 50% bioavailability correction factor) was added to the EAR for adult women using the formula 0.78 L (volume) x 85 µg/L (concentration) x 2 (for bioavailability) = 133 µg/day (+ 320 µg/day). The RDI was estimated assuming a CV of 10% for the EAR.

UPPER LEVEL OF INTAKE - DIETARY FOLATE EQUIVALENTS

Infants	
0–12 months	**Not possible to establish for supplemental folic acid. Source of intake should be milk, formula and food only**
ULs from fortified foods or supplements	
Children and adolescents	
1–3 yr	**300 µg/day as folic acid**
4–8 yr	**400 µg/day as folic acid**
9–13 yr	**600 µg/day as folic acid**
14–18 yr	**800 µg/day as folic acid**
Adults 19+ yr	
Men	**1,000 µg/day as folic acid**
Women	**1,000 µg/day as folic acid**
Pregnancy	
14–18 yr	**800 µg/day as folic acid**
19–50 yr	**1,000 µg/day as folic acid**
Lactation	
14–18 yr	**800 µg/day as folic acid**
19–50 yr	**1,000 µg/day as folic acid**

***Rationale*:** No adverse effects have been associated with consumption of the amounts of dietary folate equivalents normally found in foods or fortified foods (Butterworth & Tamura 1989). High supplemental intakes of folic acid have been shown to be related to adverse neurological effects in people with B_{12} deficiency as they can precipitate or exacerbate the B_{12} deficiency (Israels & Wilkinson 1949, Schwartz et al 1950, Spies et al 1948, Will et al 1959). General toxicity (Hunter et al 1970), increased carcinogenesis (Selby et al 1989) and adverse reproductive and developmental effects have also been reported (Czeizel & Dudas 1992, Czeizel et al 1994, Holmes-Siedle et al 1992, Kirke et al 1992, Lawrence et al 1981, Mukerjee et al 1984, Smithells et al 1981, Vergel et al 1990, Wald et al 1991).

In line with the FNB:IOM (1998) findings, setting of the LOAEL was based on the neurological effects seen with B_{12} deficiency, as this is a fairly common deficiency in the population and as these data have some dose-response characteristics. A LOAEL of 5 mg/day was set on the basis of the studies described above, as there were 100 cases of neurological damage above this level but only 8 below. A UF of 5 was used as the dose-response data were not well controlled, the adverse effects are severe and a LOAEL only, rather than a NOAEL, was available.

The UL was therefore estimated to be 1 mg folic acid (1,000 µg)/day for adults. There are no data to suggest increased susceptibility in pregnancy or lactation, so the adult UL was applied to these groups as well. There is little direct evidence for other ages, so the UL was set on a relative body weight basis for children and adolescents. It was not possible to set a UL for infants.

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