

## **Folic Acid**

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### *Function*

The term “folic acid” is used to denote pteroylmonoglutamic acid. The term “folate” refers to the naturally occurring folates in foods, which are pteroylpolyglutamic acids with two to eight glutamic acid groups attached to the primary structure (Herbert 1999). Folic acid is active as a dietary component, but must be metabolized to the reduced dihydrofolate and tetrahydrofolate forms for biological activity. The active (dihydrofolate and tetrahydrofolate) forms of folic acid are involved in a wide variety of biochemical reactions, particularly one-carbon metabolic reactions. A deficiency of folic acid impairs DNA synthesis and cell division; the common clinical manifestation of severe folic acid deficiency is megaloblastic anemia, which is hematologically similar to the anemia resulting from vitamin B<sub>12</sub> deficiency.

Food folates must be deconjugated—that is, most glutamic acid groups must be removed from them—by the intestinal enzyme folate conjugase before absorption can occur. After absorption, reduction of the dihydrofolate or tetrahydrofolate forms is necessary for biological activity. Following intestinal uptake, dietary folic acid is activated in the same manner. The folic acid activity of dietary folates and folic acid depends on the efficiency of absorption, the efficiency of conversion of folates to folic acid, and the relative molecular weights of food folates and folic acid. Currently, folate requirements are expressed as Dietary Folate Equivalents (DFE) (Food and Nutrition Board 1998), with 1 µg DFE equal to 1 µg of food folates, 0.5 µg of folic acid taken on an empty stomach, or 0.6 µg of folic acid taken with meals.

There is clear evidence that sufficient maternal dietary folic acid intake before conception and very early in pregnancy can decrease the risk of having babies with neural tube birth defects (NTD), which include spina bifida, anencephaly, and encephalocele (Food and Drug Administration 1993). All the clinical trial evidence showing a reduced risk of NTD relates to supplemental folic acid, but the health claim authorized for the U.S. by FDA is related to total “folate,” or naturally occurring food folates and folic acid from fortified foods or dietary supplements. The daily intake of folic acid shown to be effective for this purpose is 400 µg (0.4 mg) or higher, an amount above the RDA in most countries. Although folic acid can reduce the risk for NTD, these defects are not solely attributable to folic acid deficiency. Folic acid supplementation generally reduces the risk by 50 to 75 percent.

Substantial evidence indicates that sufficient dietary folic acid can decrease the plasma concentration of homocysteine, a substance that is gaining scientific

recognition as a risk factor for heart disease (Boushey et al. 1995; den Heijer et al. 1996; Malinow 1996; Food and Nutrition Board 1998). The data are not yet sufficient to make a reliable estimate of the amount of folic acid needed to generate the health benefits, but the levels identified as possibly effective are in the same range as those shown to be effective against NTD.

## **Safety Evidence**

No adverse effects have been associated with consumption of food folates or folic acid in fortified foods (Food and Nutrition Board 1998). Three primary concerns have been identified as possible adverse effects from excessive levels of supplemental folic acid intake: (1) the masking of pernicious anemia, which allows the neurological disease of vitamin B<sub>12</sub> deficiency to progress unchecked, (2) the disruption of zinc function, and (3) the antagonism of medications, especially antifolate agents. Each of these consequences presents serious concerns and warrants careful consideration of the evidence. The evidence is weak to nonexistent that folic acid has adverse effects by any mechanism other than these three (Campbell 1996).

### **Neurological effects from masking of vitamin B<sub>12</sub> deficiency**

The administration of high levels of folic acid to patients with pernicious anemia can mask anemic manifestations while allowing neurological disease (posterolateral spinal cord degeneration) to progress (Butterworth and Tamura 1989). Fortunately, this devastating complication is not known to occur with the amounts of folic acid intake obtained through ordinary diets or through the levels of intake contained in the vast majority of dietary supplements. The more convincing reports of the masking effect involve administration of 5 mg or more of folic acid per day. A few early reports showed some response in certain hematological indices for pernicious anemia patients taking folic acid doses as low as 0.1 mg to 0.8 mg. These effects are sometimes interpreted as indicating possible risk from increased folic acid intake (Savage and Lindenbaum 1995). The risk, however, is speculative because more than 25 percent of vitamin B<sub>12</sub>-deficient patients who are not taking folic acid do not have anemia (normal hematocrit and normal mean cell volume) but only neurological signs (Healton et al. 1991). Thus, a report of an individual with neurological signs of vitamin B<sub>12</sub> deficiency who has also taken folic acid supplements (Brantigan 1997) does not necessarily show evidence of a masking effect. There is no clear evidence that folic acid changes the timing or neurological outcome of vitamin B<sub>12</sub> deficiency. Although there are a few reports of an incomplete masking effect resulting from amounts of folic acid smaller than 1 mg, the effect is unusual at that intake and is predictable only at 5 mg or more (Food and Drug Administration 1993). In addition, many pernicious anemia patients who respond to folic acid may also be deficient in folic acid (Dudley and Coltman 1970). Although hemoglobin and hematocrit respond in some patients, particularly those receiving high oral doses

or parenteral administration, folic acid does not completely normalize hematological morphology in vitamin B<sub>12</sub> deficiency (Herbert 1963).

### **Folic acid-zinc interactions**

Certain folic acid-zinc interactions are well documented. The folate conjugase enzyme must act on food pteroylpolyglutamates for absorption, which does not occur in zinc deficiency (Butterworth and Tamura 1989). The crucial issue, however, is whether higher intakes of folic acid have adverse consequences through a disruption of zinc bioavailability or function, and, if so, what the levels of folic acid associated with such effects are. Some reports suggest that as little as 350 µg of supplemental folic acid can adversely affect zinc nutriture (Mukherjee et al. 1984; Milne et al. 1984; Simmer et al. 1987), but more recent reports indicate no adverse effects of folic acid on zinc uptake or function (Tamura et al. 1992; Kauwell et al. 1995).

The suggestion that folic acid intakes of less than 400 µg (0.4 mg) per day can negatively affect pregnancy through the antagonism of zinc functions (Mukherjee et al. 1984) was not supported by a large, multi-center study involving a tenfold higher folic acid intake throughout pregnancy (Wald et al. 1991).

It is difficult to resolve differences in the scientific literature regarding a possible adverse effect of folic acid on zinc nutriture. These incompatible results can likely be attributed to the widely different experimental approaches used. In general, methods based on uptake rate and plasma concentration tend to show effects at lower folic acid intakes, whereas zinc balance methods tend to show effects only at higher intakes. Large, well-conducted clinical trials have found no adverse effects of folic acid on pregnancy through zinc antagonism or any other mechanism, but they have demonstrated a clear benefit in reducing the risk of NTD (Wald et al. 1991; Czeizel and Dudas 1992).

### **Folic acid-drug interactions**

At very high levels of intake, folic acid has been reported to interfere with the effectiveness of anticonvulsant drugs such as diphenylhydantoin, which is used in controlling epilepsy (Food and Drug Administration 1993). Oral folic acid doses of 5 to 30 mg have produced some evidence of increased frequency of seizures in epileptics, but there is no evidence of such effects at lower intakes of folic acid. It might be expected that increased folic acid intakes could interfere with actions of folate antagonistic drugs such as methotrexate. Conversely, administration of 1 mg of folic acid daily for six months in patients with rheumatoid arthritis who were treated with low-dose methotrexate actually decreased methotrexate toxicity without affecting the drug's therapeutic efficacy (Morgan et al. 1990).

## **Published Official Reviews of Folic Acid Safety**

The FNB established a UL of 1,000 µg for free folic acid, based on identification of a LOAEL of 5,000 µg and selection of a UF of 5 (Food and Nutrition Board 1998). The LOAEL was based on neurological manifestations in patients receiving 5 mg or more of folic acid without supplemental vitamin B<sub>12</sub>. The FNB declined to identify a NOAEL, although many of the studies it cited failed to find adverse effects at doses of 1 to 1.25 mg folic acid. There is no record of adverse effects caused by food polyglutamyl folates, perhaps because of the lower bioavailability and/or the limited range of intakes observed. No studies have been done with elevated doses of purified polyglutamyl folates. Thus, the UL applies to purified folic acid only.

Like FNB, EC SCF established a UL of 1,000 µg for folic acid, basing its finding apparently on both a LOAEL of 5,000 µg and a UF of 5, and also on a NOAEL of 1,000 µg and a UF of 1 (Scientific Committee on Food 2000). In addition to identifying adverse effects at dosages above 5 mg, EC SCF concluded that “dosages of up to 1 mg of folic acid are unlikely to cause masking of the hematological signs in PA patients.” The resulting UL is 1,000 µg of free folic acid, but this value does not apply to the polyglutamyl folates found naturally in foods.

Similar to FNB and EC SCF, UK EVM established a GL of 1,000 µg of free folic acid (Expert Group on Vitamins and Minerals 2003). This value was based on both a NOAEL of 1 mg and a LOAEL of 5 mg, with UF values applied that produced the UL of 1,000 µg. The UK EVM considered the entire dataset to be uncertain enough to preclude setting SUL values, but nevertheless its GL was derived using the SUL method.

## **CRN ULS for Folic Acid**

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A folic acid supplement of 4 mg per day (4,000 µg) was used without adverse effect in a seven-nation trial that involved a total of 1,817 women at thirty-three study centers (Wald et al. 1991). A committee advising the FDA on folic acid and NTD concluded that adverse effects were unlikely with intakes of 1,000 µg (1 mg) or less (Food and Drug Administration 1996). The evidence that intakes of 1,000 µg (1 mg) of total folic acid plus food folates are without identifiable risk of any known adverse effects is sufficient to identify this level as the NOAEL. This conclusion is consistent with the advice of FDA’s Food Advisory Committee and the U.S. Public Health Service, but may be more related to cautious policy than to scientific evidence. Reports of adverse effects from lower intakes of folic acid have been contradicted by subsequent studies, and therefore these reports are not

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useful in the identification of a NOAEL or a LOAEL. Some data suggest that the LOAEL might be 5,000 mg.

Two studies found no significant increase in risk of masking neurological effects with folic acid doses of 1.25 mg per day (Ross et al. 1948; Chodos and Ross 1951), whereas there is some evidence that masking may be a problem with intakes of 1.5 and 2.55 mg (Victor and Lear 1956). On the basis of the absence of adverse effects at 1,000 µg and no significant effects at up to 1.25 mg, CRN sets its UL for supplemental folic acid at 1,000 µg. The identification of a LOAEL at 5,000 µg by FNB, EC SCF and UK EVM, together with the absence of any data that would suggest a LOAEL lower than 1.5 or 2.55 mg, provides a margin of safety to allow for intakes of folic acid-fortified foods. Therefore the 1,000 µg NOAEL may be applied to supplemental folic acid, making the CRN ULS for folic acid also 1,000 µg.

### **Comparison of Safety Values for Folic Acid**

<b>CRN ULS</b>	1,000 µg
<b>US FNB UL</b>	1,000 µg
<b>EC SCF UL</b>	1,000 µg
<b>EC supplement maximum</b>	Not established (as of May 2004)
<b>UK EVM GL, supplement</b>	1,000 µg

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