Folic Acid

Introduction

The term "folic acid" is used to denote pteroylmonoglutamic acid or vitamin B_9. "Folate" indicates the naturally occurring compounds in foods that are aromatic pteridine rings linked to para-aminobenzoic acid with 2 to 8 glutamic acid groups attached to the primary structure (Herbert 1999). Folic acid is used as a dietary component (i.e., in food fortification and dietary supplements) 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 (larger than normal but fewer red blood cells) anemia, which is hematologically similar to the anemia resulting from vitamin B_{12} deficiency.

There is clear evidence that sufficient maternal dietary folic acid before conception and very early in pregnancy (within the first 28 days postfertilization) can decrease the risk of having babies with neural tube birth defects (NTDs), which include spina bifida, anencephaly, and encephalocele (Food and Drug Administration [FDA] 1993a, 1993b). All the clinical trial evidence showing a reduced risk of NTDs relates to supplemental folic acid, but the health claim authorized for the United States by the FDA is related to "total folate," or naturally occurring food folates plus 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 NTDs, these defects are not solely attributable to folic acid deficiency. Folic acid supplementation generally reduces the risk by 50 to 75 percent.

Preliminary evidence suggests that sufficient dietary folic acid can decrease the plasma concentration of homocysteine, a substance that is gaining scientific recognition as a causative risk factor for heart disease (Boushey et al. 1995; den Heijer et al. 1996; Malinow 1996; Institute

of Medicine [IOM] 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 NTDs.

Bioavailability

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 to the dihydrofolate or tetrahydrofolate forms is necessary for biological activity. Following absorption, dietary folic acid is activated in the same manner as diet-derived folates. 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) (IOM 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. These differences reflect the relative bioavailability of folic acid versus folate; folic acid added to foods during fortification or supplementation is 70 to 85 percent bioavailable compared with 50 percent of folate occurring naturally in foods (Hoyo et al. 2011).

Safety Considerations

No adverse effects have been associated with consumption of food folates or folic acid in fortified foods or dietary supplements (IOM 1998). Folates and folic acid are water soluble and thus excretion is relatively straightforward. 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_{12} deficiency to progress unchecked; (2) the disruption of zinc function; and (3) the antagonism of medications, especially antifolate agents such as methotrexate. 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; European Commission, Scientific Committee on Food [EC SCF] 2000).

Neurological Effects from Masking of Vitamin B_{12} 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; IOM 1998; National Institutes of Health [NIH] 2012). 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 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 to 0.8 mg. These effects are sometimes interpreted as indicating possible risk from increased folic acid intakes (Savage and Lindenbaum 1995). The risk, however, is speculative because more than 25 percent of vitamin B_{12}-deficient patients who are not taking folic acid did 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_{12} deficiency who has also taken folic acid supplements (Brantigan 1997) does not conclusively show evidence of a masking effect.

There is no clear evidence that folic acid changes the time course or neurological outcome of vitamin B_{12} 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 (FDA 1993a, 1993b). In addition, many pernicious anemia patients who respond to folic acid may also be deficient in folic acid (Dudley and Coltman 1970). Hemoglobin and hematocrit respond to folic acid administration in some patients, particularly those receiving folic acid in high oral doses or through parenteral administration. Regardless of this effect, folic acid does not completely normalize hematological morphology in vitamin B_{12} 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 is reduced 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 (Milne et al. 1984; Mukherjee 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, multicenter 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. The 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 NTDs (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 (FDA 1993a, 1993b). 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 folic acid

daily for 6 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).

Official Reviews

IOM (1998). The IOM 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. The LOAEL was based on neurological manifestations in patients receiving 5 mg or more folic acid without supplemental vitamin B_{12}. The IOM 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, either in fortified foods or in dietary supplements.

EC SCF (2000). Like the IOM, the 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 (EC SCF 2000). In addition to identifying adverse effects at dosages above 5 mg, the 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.

Expert Group on Vitamins and Minerals (EVM 2003). Similar to the IOM and the EC SCF, the UK's EVM established a guidance level of 1,000 µg of free folic acid (EVM 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 EVM considered the entire dataset to be uncertain enough to preclude setting SUL values, but its guidance level was derived using the SUL method and was applied in that manner.

CRN Recommendations

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 33 study centers (Wald et al. 1991). A committee advising the FDA on folic acid and NTDs concluded that adverse effects were unlikely with intakes of 1,000 µg (1 mg) or less (FDA 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 the 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 useful in the identification of a NOAEL or a LOAEL. Some data suggest that the LOAEL might be 5,000 mg.

The 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 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 the IOM, the EC SCF, and the 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 UL for supplements of folic acid 1,000 µg.

Quantitative Summary for Folic Acid

CRN UL, supplemental intake	1,000 μg/day
IOM UL, total intake	1,000 μg/day
EC SCF UL, total intake	1,000 μg/day
EC supplement maximum	Not determined
EVM, guidance level, supplemental intake	1,000 μg/day

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