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Rationale for Replacing Folic Acid with NatureFolate™

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Introduction

Folate is a generic term for a group of water soluble b-vitamins that includes folic acid and naturally occurring folates in food. The terms "folic acid" and "folate" are often used interchangeably, but more appropriately, folic acid refers to the fully oxidized synthetic compound (pteroylmonoglutamic acid) used in dietary supplements and in food fortification while folate refers to the various tetrahydrofolate derivatives naturally present in foods.[1, 2] Folic acid got its name from folium, the Latin word for leaf when it was isolated from spinach in 1941.[1]

Humans are unable to make their own folate, making it an essential nutrient that is typically obtained from the diet.[3] Important sources of folate are leafy green vegetables, fruits, legumes, liver, eggs, dairy products, and orange juice. Food folates are mainly pteroylpolyglutamate forms of tetrahydofolate, 5-methyl-tetrahydrofolate (5-MTHF), 10-formyltetrahydrofolate and 5-formyltetrahydrofolate.[4, 5] Folic acid, which is again, the fully oxidized synthetic compound (pteroylmonoglutamic acid), is obtained in the diet mainly from folic acid-fortified grain products and folic acid-containing supplements. Unlike any of the natural folates in foods that are in reduced forms, folic acid is a fully oxidized compound. Human exposure to this form was non-existent until its chemical synthesis (1943) and use in food fortification (1998) and dietary supplements.[6] The small amount of folic acid that can be isolated from cells occurs through the in vitro oxidation of natural tetrahydrofolates.[7]

There are three forms of folate currently used in dietary supplements: 1) folic acid, a fully oxidized synthetic chemical compound; 2) folinic acid, also known as 5-formyl- tetrahydrofolic acid, leucovorin calcium and calcium folinate, and 3) methyl folate, also known as the calcium salt of 5-methyltetrahydrofolic acid.[8, 9] Folic acid is the most commonly used form in dietary supplements since its synthesis, due to its stability and lower cost.[1, 7] Folinic acid has been the standard adjunct to anti-cancer drugs such as methotrexate and 5-fluorouracil.[10, 11] Following the development of the stable form of folinic acid, calcium folinate, it has found use in dietary supplements.[8] More recently 5-MTHF has become available for use in dietary supplements.[7, 9] A manufacturer that holds rights to several patents covering the use of 5-MTHF in foods has imposed stringent restrictions in the use of 5-MTHF in dietary supplements, such as specifying what formulas and dosages can be used, consequently preventing the general use of 5-MTHF in dietary supplements.

Health Concerns with Folic Acid

Folates are essential cofactors in one carbon metabolism and their deficiency is associated with health risks such as neural tube defects, cancers and hyperhomocysteinemia.[2, 12, 13] Following the discovery and synthesis of folic acid, it has been demonstrated that folic acid supplementation can greatly reduce the incidence and recurrence of neural tube defects.[14, 15] This led to the mandatory fortification of cereal-grain products with folic acid in the USA and Canada.[16, 17] Since then, studies reported many health benefits of folic acid fortification.[18-20] However, there were also studies that raised concern over the safety of chronically high intake of folic acid from fortified foods, beverages and dietary supplements.[6, 21, 22] It has been shown that many breakfast cereals are over-fortified with folic acid, that when consumed with other folic acid-containing beverages and dietary supplements, could result in intakes that greatly exceed recommended daily doses.[21, 23-25]

The risk of higher than desired folic acid intake is compounded by concerns over the appearance of unmetabolized (unaltered) folic acid (pteroylmonoglutamic acid) in the blood circulatory system.[22, 26] It has been demonstrated that even a modest intake of less than 400 micrograms per day of folic acid from fortified foods or supplements may lead to the appearance of umetabolized folic acid in the bloodstream.[27-29] Unlike the natural folates (e.g., 5-methyltetrahydrofolate and 5-formyltetrahydrofolate), folic acid is not a normal metabolite and must be reduced to dihydrofolate and then to tetrahydrofolate, the form that can enter the folate cycle.[7, 26] The low dihydrofolate reductase activity in human liver, where folic acid is first metabolized, could be saturated following even a modest or repeated dietary intake of folic acid, resulting in unmetabolized folic acid entering the systemic circulation.[22, 26]

The health outcomes of chronic exposure to unmetabolized folic acid have not been evaluated and several papers recommend that long term studies on the safety of folic acid be conducted.[6, 21, 30] There are several studies that seem to indicate potential risk of folic acid intake.[31-36] One study showed an apparent increase in the incidence of colorectal cancer after the mandatory fortification of folic acid in both the USA and Canada.[35] There is a growing body of evidence that seems to suggest the dual role of folates in carcinogenesis. High folate status prevents cancer development in the absence of preneoplastic lesions, but folic acid supplementation promotes the growth and development of existing preneoplastic lesions.[30, 37, 38]

Another concern with folic acid intake is associated with accelerated cognitive decline in older persons. One paper reported that persons who consumed folic acid in excess of 400 micrograms per day had a significantly faster rate of cognitive decline than supplement non-users, possibly due to masking of unrecognized B12 deficiency.[31] The elderly are known to often have compromised B12 status and consequently could be at greater risk for cognitive decline.[36]

NatureFolate™

Researchers at Designs for Health thoroughly reviewed hundreds of papers on folic acid and have decided that the fully oxidized, synthetic form is not the ideal choice for nutritional supplement formulations. DFH is replacing folic acid with a natural folate blend called NatureFolate™. NatureFolate™ is made from a concentrated vegetable juice powder containing a blend of natural folates, including 5-methyltetrahydrofolate (5-MTHF) and 5-formyltetrahydrofolate with additional fortified 5-formyltetrahydrofolate as calcium folinate.

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