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Folate: What is it?

Folate is a water-soluble B vitamin that occurs naturally in food. **Folic acid** is the synthetic form of folate that is found in supplements and added to fortified foods [1].

Folate gets its name from the Latin word "folium" for leaf. A key observation of researcher Lucy Wills nearly 70 years ago led to the identification of folate as the nutrient needed to prevent the anemia of pregnancy. Dr. Wills demonstrated that the anemia could be corrected by a yeast extract. Folate was identified as the corrective substance in yeast extract in the late 1930s, and was extracted from spinach leaves in 1941.

Folate helps produce and maintain new cells [2]. This is especially important during periods of rapid cell division and growth such as infancy and pregnancy. Folate is needed to make DNA and RNA, the building blocks of cells. It also helps prevent changes to DNA that may lead to cancer [3]. Both adults and children need folate to make normal red blood cells and prevent anemia [4]. Folate is also essential for the metabolism of homocysteine, and helps maintain normal levels of this amino acid.

What foods provide folate?

Leafy green vegetables (like spinach and turnip greens), fruits (like citrus fruits and juices), and dried beans and peas are all natural sources of folate [5].

In 1996, the Food and Drug Administration (FDA) published regulations requiring the addition of folic acid to enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products [6-9]. Since cereals and grains are widely consumed in the U.S., these products have become a very important contributor of folic acid to the American diet. The following table suggests a variety of dietary sources of folate.

Table 1: Selected Food Sources of Folate and Folic Acid [5]

Food	Micrograms (µg)	% DV [^]
*Breakfast cereals fortified with 100% of the DV, ¾ cup	400	100
Beef liver, cooked, braised, 3 ounces	185	45
Cowpeas (blackeyes), immature, cooked, boiled, ½ cup	105	25
*Breakfast cereals, fortified with 25% of the DV, ¾ cup	100	25
Spinach, frozen, cooked, boiled, ½ cup	100	25
Great Northern beans, boiled, ½ cup	90	20
Asparagus, boiled, 4 spears	85	20
*Rice, white, long-grain, parboiled, enriched, cooked, ½ cup	65	15
Vegetarian baked beans, canned, 1 cup	60	15
Spinach, raw, 1 cup	60	15
Green peas, frozen, boiled, ½ cup	50	15
Broccoli, chopped, frozen, cooked, ½ cup	50	15
*Egg noodles, cooked, enriched, ½ cup	50	15
Broccoli, raw, 2 spears (each 5 inches long)	45	10
Avocado, raw, all varieties, sliced, ½ cup sliced	45	10
Peanuts, all types, dry roasted, 1 ounce	40	10
Lettuce, Romaine, shredded, ½ cup	40	10
Wheat germ, crude, 2 Tablespoons	40	10
Tomato Juice, canned, 6 ounces	35	10
Orange juice, chilled, includes concentrate, ¾ cup	35	10
Turnip greens, frozen, cooked, boiled, ½ cup	30	8
Orange, all commercial varieties, fresh, 1 small	30	8

*Bread, white, 1 slice	25	6
*Bread, whole wheat, 1 slice	25	6
Egg, whole, raw, fresh, 1 large	25	6
Cantaloupe, raw, ¼ medium	25	6
Papaya, raw, ½ cup cubes	25	6
Banana, raw, 1 medium	20	6

* Items marked with an asterisk (*) are fortified with folic acid as part of the Folate Fortification Program.

^ DV = Daily Value. DVs are reference numbers developed by the Food and Drug Administration (FDA) to help consumers determine if a food contains a lot or a little of a specific nutrient. The DV for folate is 400 micrograms (µg). Most food labels do not list a food's magnesium content. The percent DV (%DV) listed on the table indicates the percentage of the DV provided in one serving. A food providing 5% of the DV or less is a low source while a food that provides 10-19% of the DV is a good source. A food that provides 20% or more of the DV is high in that nutrient. It is important to remember that foods that provide lower percentages of the DV also contribute to a healthful diet. For foods not listed in this table, please refer to the U.S. Department of Agriculture's Nutrient Database Web site: http://www.nal.usda.gov/fnic/cgi-bin/nut_search.pl.

What are the Dietary Reference Intakes for folate?

Recommendations for folate are given in the Dietary Reference Intakes (DRIs) developed by the Institute of Medicine of the National Academy of Sciences [10]. *Dietary Reference Intakes* is the general term for a set of reference values used for planning and assessing nutrient intake for healthy people. Three important types of reference values included in the DRIs are Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels (UL). The RDA recommends the average daily intake that is sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in each age and gender group [10]. An AI is set when there is insufficient scientific data available to establish a RDA. AIs meet or exceed the amount needed to maintain a nutritional state of adequacy in nearly all members of a specific age and gender group. The UL, on the other hand, is the maximum daily intake unlikely to result in adverse health effects [10].

The RDAs for folate are expressed in a term called the Dietary Folate Equivalent. The Dietary Folate Equivalent (DFE) was developed to help account for the differences in absorption of naturally occurring dietary folate and the more bioavailable synthetic folic acid [10-11]. Table 2 lists the RDAs for folate, expressed in micrograms (µg) of DFE, for children and adults [10].

Table 2: Recommended Dietary Allowances for Folate for Children and Adults [10]

Age (years)	Males and Females (µg/day)	Pregnancy (µg/day)	Lactation (µg/day)
1-3	150	N/A	N/A
4-8	200	N/A	N/A
9-13	300	N/A	N/A
14-18	400	600	500
19+	400	600	500

*1 DFE = 1 µg food folate = 0.6 µg folic acid from supplements and fortified foods

There is insufficient information on folate to establish an RDA for infants. An Adequate Intake (AI) has been established that is based on the amount of folate consumed by healthy infants who are fed breast milk [10]. Table 3 lists the Adequate Intake for folate, in micrograms (µg), for infants.

Table 3: Adequate Intake for folate for infants [10]

Age (months)	Males and Females (µg/day)
0 to 6	65
7 to 12	80

The National Health and Nutrition Examination Survey (NHANES III 1988-94) and the Continuing Survey of Food Intakes by Individuals (1994-96 CSFII) indicated that most individuals surveyed did not consume adequate folate [12-13]. However, the folic acid fortification program, which was initiated in 1998, has increased folic acid content of commonly eaten foods such as cereals and grains, and as a result most diets in the United States (US) now provide recommended amounts of folate equivalents [14].

When can folate deficiency occur?

A deficiency of folate can occur when an increased need for folate is not matched by an increased intake, when dietary folate intake does not meet recommended needs, and when folate loss increases. Medications that interfere with the metabolism of folate may also increase the need for this vitamin and risk of deficiency [1,15-].

Medical conditions that increase the need for folate or result in increased loss of folate include:

- pregnancy and lactation (breastfeeding)
- alcohol abuse
- malabsorption
- kidney dialysis
- liver disease
- certain anemias

Medications that interfere with folate utilization include:

- anticonvulsant medications (such as dilantin, phenytoin and primidone)
- metformin (sometimes prescribed to control blood sugar in type 2 diabetes)
- sulfasalazine (used to control inflammation associated with Crohn's disease and ulcerative colitis)
- triamterene (a diuretic)
- methotrexate (used for cancer and other diseases such as rheumatoid arthritis)
- barbiturates (used as sedatives)

What are some common signs and symptoms of folate deficiency?

- Folate deficient women who become pregnant are at greater risk of giving birth to low birth weight, premature, and/or infants with neural tube defects.
- In infants and children, folate deficiency can slow overall growth rate.
- In adults, a particular type of anemia can result from long term folate deficiency.
- Other signs of folate deficiency are often subtle. Digestive disorders such as diarrhea, loss of appetite, and weight loss can occur, as can weakness, sore tongue, headaches, heart palpitations, irritability, forgetfulness, and behavioral disorders [1,20]. An elevated level of homocysteine in the blood, a risk factor for cardiovascular disease, also can result from folate deficiency.

Many of these subtle symptoms are general and can also result from a variety of medical conditions other than folate deficiency. It is important to have a physician evaluate these symptoms so that appropriate medical care can be given.

Do women of childbearing age and pregnant women have a special need for folate?

Folic acid is very important for all women who may become pregnant. Adequate folate intake during the periconceptual period, the time just before and just after a woman becomes pregnant, protects against neural tube defects [21]. Neural tube defects result in malformations of the spine (spina bifida), skull, and brain (anencephaly) [10]. The risk of neural tube defects is significantly reduced when supplemental folic acid is consumed in addition to a healthful diet prior to and during the first month following conception [10,22-23]. Since January 1, 1998, when the folate food fortification program took effect, data suggest that there has been a significant reduction in neural tube birth defects [24]. Women who could become pregnant are advised to eat foods fortified with folic acid or take a folic acid supplement in addition to eating folate-rich foods to reduce the risk of some serious birth defects. For this population, researchers recommend a daily intake of 400 µg of synthetic folic acid per day from fortified foods and/or dietary supplements [10].

Who else may need extra folic acid to prevent a deficiency?

People who abuse alcohol, those taking medications that may interfere with the action of folate (including, but not limited to those listed above), individuals diagnosed with anemia from folate deficiency, and those with malabsorption, liver disease, or who are receiving kidney dialysis treatment may benefit from a folic acid supplement.

Folate deficiency has been observed in alcoholics. A 1997 review of the nutritional status of chronic alcoholics found low folate status in more than 50% of those surveyed [25]. Alcohol interferes with the absorption of folate and increases the amount of folate the kidney gets rid of. In addition, many people who abuse alcohol have poor quality diets that do not provide the recommended intake of folate [17]. Increasing folate intake through diet, or folic acid intake through fortified foods or supplements, may be beneficial to the health of alcoholics.

Anti-convulsant medications such as dilantin increase the need for folate [26-27]. Anyone taking anti-convulsants and other medications that interfere with the body's ability to use folate should consult with a medical doctor about the need to take a folic acid supplement [28-30].

Anemia is a condition that occurs when there is insufficient hemoglobin in red blood cells to carry enough oxygen to cells and tissues. It can result from a wide variety of medical problems, including folate deficiency. With folate deficiency, your body may make large red blood cells that do not contain adequate hemoglobin, the substance in red blood cells that carries oxygen to your body's cells [4]. Your physician can determine whether an anemia is associated with folate deficiency and whether supplemental folic acid is indicated.

Several medical conditions increase the risk of folic acid deficiency. Liver disease and kidney dialysis increase the loss of folic acid. Malabsorption can prevent your body from using folate in food. Medical doctors treating individuals with these disorders will evaluate the need for a folic acid supplement [1].

What are some current issues and controversies about folate?

Folic Acid and Cardiovascular Disease

Cardiovascular disease involves any disorder of the heart and blood vessels that make up the cardiovascular system. Coronary heart disease occurs when blood vessels which supply the heart become clogged or blocked, increasing the risk of a heart attack. Vascular damage can also occur to blood vessels supplying the brain, and can result in a stroke.

Cardiovascular disease is the most common cause of death in industrialized countries such as the US, and is on the rise in developing countries. The National Heart, Lung, and Blood Institute of the National Institutes of Health has identified many risk factors for cardiovascular disease, including an elevated LDL-cholesterol level, high blood pressure, a low HDL-cholesterol level, obesity, and diabetes [31]. In recent years, researchers have identified another risk factor for cardiovascular disease, an elevated homocysteine level. Homocysteine is an amino acid normally found in blood, but elevated levels have been linked with coronary heart disease and stroke [32-44]. Elevated homocysteine levels may impair endothelial vasomotor function, which determines how easily blood flows through blood vessels [45]. High levels of homocysteine also may damage coronary arteries and make it easier for blood clotting cells called platelets to clump together and form a clot, which may lead to a heart attack [38].

A deficiency of folate, vitamin B₁₂ or vitamin B₆ may increase blood levels of homocysteine, and folate supplementation has been shown to decrease homocysteine levels and to improve endothelial function [46-48]. At least one study has linked low dietary folate intake with an increased risk of coronary events [49]. The folic acid fortification program in the U. S. has decreased the prevalence of low levels of folate and high levels of homocysteine in the blood in middle-aged and older adults [50]. Daily consumption of folic-acid fortified breakfast cereal and the use of folic acid supplements has been shown to be an effective strategy for reducing homocysteine concentrations [51].

Evidence supports a role for supplemental folic acid for lowering homocysteine levels, however this does not mean that folic acid supplements will decrease the risk of cardiovascular disease. Clinical intervention trials are underway to determine whether supplementation with folic acid, vitamin B₁₂, and vitamin B₆ can lower risk of coronary heart disease. It is premature to recommend folic acid supplementation for the prevention of heart disease until results of ongoing randomized, controlled clinical trials positively link increased folic acid intake with decreased homocysteine levels AND decreased risk of cardiovascular disease.

Folic Acid and Cancer

Some evidence associates low blood levels of folate with a greater risk of cancer [52]. Folate is involved in the synthesis, repair, and function of DNA, our genetic map, and there is some evidence that a deficiency of folate can cause damage to DNA that may lead to cancer [52]. Several studies have associated diets low in folate with increased risk of breast, pancreatic, and colon cancer [53-54]. Over 88,000 women enrolled in the Nurses' Health Study who were free of cancer in 1980 were followed from 1980 through 1994. Researchers found that women ages 55 to 69 years in this study who took multivitamins containing folic acid for more than 15 years had a markedly lower risk of developing colon cancer [54]. Findings from over 14,000 subjects followed for 20 years suggest that men who do not consume alcohol and whose diets provide the recommended intake of folate are less likely to develop colon cancer [55]. However, associations between diet and disease do not indicate a direct cause. Researchers are continuing to investigate whether enhanced folate intake from foods or folic acid supplements may reduce the risk of cancer. Until results from such clinical trials are available, folic acid supplements should not be recommended to reduce the risk of cancer.

Folic Acid and Methotrexate for Cancer

Folate is important for cells and tissues that rapidly divide [2]. Cancer cells divide rapidly, and drugs that interfere with folate metabolism are used to treat cancer. Methotrexate is a drug often used to treat cancer because it limits the activity of enzymes that need folate.

Unfortunately, methotrexate can be toxic, producing side effects such as inflammation in the digestive tract that may make it difficult to eat normally [56-58]. Leucovorin is a form of folate that can help "rescue" or reverse the toxic effects of methotrexate [59]. There are many studies underway to determine if folic acid supplements can help control the side effects of methotrexate without decreasing its effectiveness in chemotherapy [60-61]. It is important for anyone receiving methotrexate to follow a medical doctor's advice on the use of folic acid supplements.

Folic Acid and Methotrexate for Non-Cancerous Diseases

Low dose methotrexate is used to treat a wide variety of non-cancerous diseases such as rheumatoid arthritis, lupus, psoriasis, asthma, sarcoidosis, primary biliary cirrhosis, and inflammatory bowel disease [62]. Low doses of methotrexate can deplete folate stores and cause side effects that are similar to folate deficiency. Both high folate diets and supplemental folic acid may help reduce the toxic side effects of low dose methotrexate without decreasing its effectiveness [63-64]. Anyone taking low dose methotrexate for the health problems listed above should consult with a physician about the need for a folic acid supplement.

Caution About Folic Acid Supplements

Beware of the interaction between vitamin B₁₂ and folic acid

Intake of supplemental folic acid should not exceed 1,000 micrograms (µg) per day to prevent folic acid from triggering symptoms of vitamin B₁₂ deficiency [10]. Folic acid supplements can correct the anemia associated

with vitamin B₁₂ deficiency. Unfortunately, folic acid will not correct changes in the nervous system that result from vitamin B₁₂ deficiency. Permanent nerve damage can occur if vitamin B₁₂ deficiency is not treated.

It is very important for older adults to be aware of the relationship between folic acid and vitamin B₁₂ because they are at greater risk of having a vitamin B₁₂ deficiency. If you are 50 years of age or older, ask your physician to check your B₁₂ status before you take a supplement that contains folic acid. If you are taking a supplement containing folic acid, read the label to make sure it also contains B₁₂ or speak with a physician about the need for a B₁₂ supplement.

What is the health risk of too much folic acid?

Folate intake from food is not associated with any health risk. The risk of toxicity from folic acid intake from supplements and/or fortified foods is also low [65]. It is a water soluble vitamin, so any excess intake is usually lost in the urine. There is some evidence that high levels of folic acid can provoke seizures in patients taking anti-convulsant medications [1]. Anyone taking such medications should consult with a medical doctor before taking a folic acid supplement.

The Institute of Medicine has established a tolerable upper intake level (UL) for folate from fortified foods or supplements (i.e. folic acid) for ages one and above. Intakes above this level increase the risk of adverse health effects. In adults, supplemental folic acid should not exceed the UL to prevent folic acid from triggering symptoms of vitamin B₁₂ deficiency [10]. It is important to recognize that the UL refers to the amount of synthetic folate (i.e. folic acid) being consumed per day from fortified foods and/or supplements. There is no health risk, and no UL, for natural sources of folate found in food. Table 4 lists the Upper Intake Levels (UL) for folate, in micrograms (µg), for children and adults.

Table 4: Tolerable Upper Intake Levels for Folate for Children and Adults [10]

Age (years)	Males and Females (µg/day)	Pregnancy (µg/day)	Lactation (µg/day)
1-3	300	N/A	N/A
4-8	400	N/A	N/A
9-13	600	N/A	N/A
14-18	800	800	800
19 +	1000	1000	1000

Selecting a healthful diet

As the 2000 *Dietary Guidelines for Americans* states, "Different foods contain different nutrients and other healthful substances. No single food can supply all the nutrients in the amounts you need" [66]. As indicated in Table 1, green leafy vegetables, dried beans and peas, and many other types of vegetables and fruits provide folate. In addition, fortified foods are a major source of folic acid. It is not unusual to find foods such as some ready-to-eat cereals fortified with 100% of the RDA for folate. The variety of fortified foods available has made it easier for women of childbearing age in the US to consume the recommended 400 mcg of folic acid per day from fortified foods and/or supplements [6]. The large numbers of fortified foods on the market, however, also raises the risk of exceeding the UL. This is especially important for anyone at risk of vitamin B₁₂ deficiency, which can be triggered by too much folic acid. It is important for anyone who is considering taking a folic acid supplement to first consider whether their diet already includes adequate sources of dietary folate and fortified food sources of folic acid.

For more information about building a healthful diet, refer to the Dietary Guidelines for Americans (<http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2000/2000DGPProfessionalBooklet.pdf>) [66] and the US Department of Agriculture's Food Guide Pyramid (<http://www.nal.usda.gov/fnic/fpyr/pyramid.html>) [67].

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