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]

<table>
<thead>
<tr>
<th>Food</th>
<th>Micrograms (μg)</th>
<th>% DV^</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Breakfast cereals fortified with 100% of the DV, ¾ cup</td>
<td>400</td>
<td>100</td>
</tr>
<tr>
<td>Beef liver, cooked, braised, 3 ounces</td>
<td>215</td>
<td>54</td>
</tr>
<tr>
<td>Lentils, mature seeds, cooked, boiled, ½ cup</td>
<td>179</td>
<td>45</td>
</tr>
<tr>
<td>Spinach, frozen, cooked, boiled, ½ cup</td>
<td>115</td>
<td>29</td>
</tr>
<tr>
<td>*Egg noodles, cooked, enriched, ½ cup</td>
<td>110</td>
<td>28</td>
</tr>
<tr>
<td>*Breakfast cereals fortified with 25% of the DV, ¾ cup</td>
<td>100</td>
<td>23</td>
</tr>
<tr>
<td>Great Northern beans, boiled, ½ cup</td>
<td>90</td>
<td>23</td>
</tr>
<tr>
<td>Asparagus, boiled, 4 spears</td>
<td>89</td>
<td>22</td>
</tr>
<tr>
<td>*Macaroni, cooked, enriched, ½ cup</td>
<td>84</td>
<td>21</td>
</tr>
<tr>
<td>*Rice, white, long-grain, enriched, cooked, ½ cup</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>Avocado, raw, all varieties, sliced, ½ cup</td>
<td>59</td>
<td>15</td>
</tr>
<tr>
<td>Spinach, raw, 1 cup</td>
<td>58</td>
<td>15</td>
</tr>
<tr>
<td>Papaya, raw, 1 cup cubes</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>Corn, sweet, yellow, canned ½ cup</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>Broccoli, chopped, frozen, cooked, ½ cup</td>
<td>51</td>
<td>13</td>
</tr>
<tr>
<td>Tomato Juice, canned, 1 cup</td>
<td>49</td>
<td>12</td>
</tr>
<tr>
<td>Green peas, frozen, boiled, ½ cup</td>
<td>47</td>
<td>12</td>
</tr>
<tr>
<td>Orange juice, chilled, includes concentrate, 1 cup</td>
<td>47</td>
<td>12</td>
</tr>
<tr>
<td>*Bread, white, 1 slice</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>Peanuts, all types, dry roasted, 1 ounce</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Broccoli, raw, 2 spears (each 5 inches long)</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Wheat germ, crude, 2 Tablespoons</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Strawberries, raw, 1 cup</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Cantaloupe melon, raw, 1 cup cubes</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td>Lettuce, Romaine, shredded, ½ cup</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>Vegetarian baked beans, canned, 1 cup</td>
<td>30</td>
<td>8</td>
</tr>
</tbody>
</table>
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]

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males and Females</th>
<th>Pregnancy</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(μg/day)</td>
<td>(μg/day)</td>
<td>(μg/day)</td>
</tr>
<tr>
<td>1–3</td>
<td>150</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4–8</td>
<td>200</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>9–13</td>
<td>300</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>14–18</td>
<td>400</td>
<td>600</td>
<td>500</td>
</tr>
<tr>
<td>19+</td>
<td>400</td>
<td>600</td>
<td>500</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Males and Females (μg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6</td>
<td>65</td>
</tr>
<tr>
<td>7 to 12</td>
<td>80</td>
</tr>
</tbody>
</table>

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 [1,15-19].

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 periconceptional 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 folate 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 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]**

<table>
<thead>
<tr>
<th>Age</th>
<th>Males and Females</th>
<th>Pregnancy</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(μg/day)</td>
<td>(μg/day)</td>
<td>(μg/day)</td>
</tr>
<tr>
<td>1–3</td>
<td>300</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4–8</td>
<td>400</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>9–13</td>
<td>600</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>14–18</td>
<td>800</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td>19+</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
</tr>
</tbody>
</table>

**Folate and Healthful Diets**

The federal government’s 2010 *Dietary Guidelines for Americans* notes that “nutrients should come primarily from foods. Foods in nutrient-dense, mostly intact forms contain not only the essential vitamins and minerals that are often contained in nutrient supplements, but also dietary fiber and other naturally occurring substances that may have positive health effects. ...Dietary supplements...may be advantageous in specific situations to increase intake of a specific vitamin or mineral.”

For more information about building a healthful diet, refer to the *Dietary Guidelines for Americans* and the U.S. Department of Agriculture’s food guidance system, MyPlate.

The *Dietary Guidelines for Americans* describes a healthy diet as one that:

- Emphasizes a variety of fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products. Asparagus, broccoli, leafy green vegetables (like spinach and lettuce) and orange juice are good sources of folate. Enriched whole grain breads and cereals also provide folic acid and some ready-to-eat breakfast cereals are fortified with folic acid.
- Includes lean meats, poultry, fish, beans, eggs, and nuts. Beans, green peas, lentils and peanuts are good sources of folate.
- Is low in saturated fats, trans fats, cholesterol, salt (sodium), and added sugars.
- Stays within your daily calorie needs.

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Disclaimer
This fact sheet by the Office of Dietary Supplements provides information that should not take the place of medical advice. We encourage you to talk to your health care providers (doctor, registered dietitian, pharmacist, etc.) about your interest in, questions about, or use of dietary supplements and what may be best for your overall health. Any mention in this publication of a specific brand name is not an endorsement of the product.