Vitamin B9 (Folic acid)

Folic acid, another form of which is known as folate, is one of the B vitamins. The recommended daily intake level of folate is 400 micrograms from foods or dietary supplements. Folic acid is used to treat anemia caused by folate deficiency. It is also used as a supplement by women during pregnancy to prevent neural tube defects (NTDs) in the baby. Low levels in early pregnancy are believed to be the cause of more than half of babies born with neural tube defects. More than 50 countries use fortification of certain foods with folic acid as a measure to decrease the rate of NTDs in the population. Long term supplementation is also associated with small reductions in the risk of stroke and cardiovascular disease. It may be taken by mouth or by injection.

There are no common side effects. It is not known whether high doses over a long period of time are of concern. There are concerns that large amounts of folic acid might hide vitamin B12 deficiency. It is essential for the body to make DNA, RNA, and metabolise amino acids which are required for cell division. As humans cannot make folic acid, it is required from the diet, making it an essential vitamin.

Not consuming enough folate can lead to folate deficiency. This may result in a type of anemia in which low numbers of large red blood cells occur. Symptoms may include feeling tired, heart palpitations, shortness of breath, open sores on the tongue, and changes in the color of the skin or hair. Deficiency in children may develop within a month of poor dietary intake. In adults normal total body folate is between 10,000–30,000 micrograms (µg) with blood levels of greater than 7 nmol/L (3 ng/mL).

Folic acid was discovered between 1931 and 1943. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. The wholesale cost of supplements in the developing
The world is between 0.001 and 0.005 USD per dose as of 2014.\cite{footnote16} The term "folic" is from the Latin word folium, which means leaf.\cite{footnote17} Folates occur naturally in many foods especially dark green leafy vegetables and liver.\cite{footnote8}
Definition

Food supplement manufacturers often use the term folate for something different from "pure" folic acid: in chemistry, folate refers to the deprotonated ion, and folic acid to the neutral molecule—which both coexist in water. The International Union of Pure and Applied Chemistry and the International Union of Biochemistry and Molecular Biology state that folate and folic acid are the preferred synonyms for pteroylglutamate and pteroylglutamic acid, respectively. Folate indicates a collection of "folates" that is not chemically well-characterized, including other members of the family of pteroylglutamates, or mixtures of them, having various levels of reduction of the pteridine ring, one-carbon substitutions and different numbers of glutamate residues.

Names

Other names include vitamin B₉, vitamin B₉c, vitamin M, folacin, and pteroyl-L-glutamate.

Health effects

Pregnancy

Folic acid intake during pregnancy has been linked to a lessened risk of neural tube defects. Likewise, a meta-analysis of folic acid supplementation during pregnancy reported a 28% lower risk of newborn congenital heart defects. The United States Preventive Services Task Force recommends folic acid supplementation for all women able to become pregnant.

Devakamar reviewed long-term outcomes for live births that did not involve neural tube defects and fortification with folic acid did not have an impact on childhood survival, growth, body composition, or cognitive outcomes. Prenatal supplementation did not appear to reduce the risk of pre-term births. And there does not appear to be a correlation between maternal folic acid supplementation and an increased risk for asthma in the child.

Fertility

Folate is necessary for fertility in both men and women. It contributes to spermatogenesis. Therefore, it is necessary to receive sufficient amounts through the diet to avoid subfertility. Also, polymorphisms in genes of enzymes involved in folate metabolism could be one reason for fertility complications in some women with unexplained infertility.

Heart disease

Taking folic acid over years reduced the risk of cardiovascular disease by 4%, where another study found it did not affect cardiovascular disease, even while reducing homocysteine levels.
**Stroke**

Long-term supplementation with folic acid reduced the risk of stroke by 10%, which may be due to the role folate plays in regulating homocysteine concentration.\(^{[11]}\) The reviews indicate the risk of stroke appears to be reduced only in some individuals, but a definite recommendation regarding supplementation beyond the current RDA has not been established for stroke prevention.\(^{[28]}\) Asian populations had greater protection against stroke with folate supplementation than did European or North American subjects.\(^{[11]}\)

Observed stroke reduction is consistent with the reduction in pulse pressure produced by folate supplementation of 5 mg per day, since hypertension is a key risk factor for stroke. Folic supplements are inexpensive and relatively safe to use, which is why stroke or hyperhomocysteinemia patients are encouraged to consume daily B vitamins including folic acid.\(^{[29]}\)

**Cancer**

Studies on folic acid intake from food and folate supplementation with regards to cancer risk are based on the adequacy of chronic intake. Chronically insufficient intake of folic acid (below the recommended level of 400 micrograms per day\(^{[6]}\)) may increase the risk of colorectal, breast, ovarian, pancreas, brain, lung, cervical, and prostate cancers.\(^{[30][31][32][33]}\) Other studies showed that excessive dietary supplementation with synthetic folate may increase the risk of certain cancers, in particular prostate.\(^{[34][35]}\) A 2017 review found no relationship between taking folate supplements and cancer risk.\(^{[36]}\)

**Antifolate chemotherapy**

Folate is important for cells and tissues that rapidly divide.\(^{[37]}\) Cancer cells divide rapidly, and drugs that interfere with folate metabolism are used to treat cancer. The antifolate methotrexate is a drug often used to treat cancer because it inhibits the production of the active form of THF from the inactive dihydrofolate (DHF). However, methotrexate can be toxic,\(^{[38][39][40]}\) producing side effects, such as inflammation in the digestive tract that make it difficult to eat normally. Also, bone marrow depression (inducing leukopenia and thrombocytopenia), and acute kidney and liver failure have been reported.

Folic acid, under the drug name leucovorin, a form of folate (formyl-THF), can help "rescue" or reverse the toxic effects of methotrexate.\(^{[41]}\) Folic acid is not the same as folic acid. Folic acid supplements have little established role in cancer chemotherapy.\(^{[42][43]}\) There have been cases of severe adverse effects of accidental substitution of folic acid for folinic acid in patients receiving methotrexate cancer chemotherapy. It is important for anyone receiving methotrexate to follow medical advice on the use of folic or folinic acid supplements. The supplement of folinic acid in patients undergoing methotrexate treatment is to give cells dividing less rapidly enough folate to maintain normal cell functions. The amount of folate given is depleted by rapidly dividing cells (cancer) quickly, and so does not negate the effects of methotrexate.
Psychological

Some evidence links a shortage of folate with depression. Limited evidence from randomised controlled trials showed using folic acid in addition to SSRIs may have benefits. Research at the University of York and Hull York Medical School has found a link between depression and low levels of folate. One study by the same team involved 15,315 subjects. Folic acid supplementation affects noradrenaline and serotonin receptors within the brain, which could be the cause of folic acid's possible ability to act as an antidepressant. The exact mechanisms involved in the development of schizophrenia and depression are not entirely clear, but the bioactive folate, methyltetrahydrofolate (5-MTHF), a direct target of methyl donors like S-adenosyl methionine (SAMe), recycles the inactive dihydrobiopterin (BH2) into tetrahydrobiopterin (BH4), the necessary cofactor in various steps of monoamine synthesis, including that of dopamine. BH4 serves a regulatory role in monoamine neurotransmission and is required to mediate the actions of most antidepressants. 5-MTHF also plays both direct & indirect roles in DNA methylation, NO2 synthesis, and one-carbon metabolism.

Age related macular degeneration

A sub study of the Women’s Antioxidant and Folic Acid Cardiovascular Study published in 2009 reported use of a nutritional supplement containing folic acid, pyridoxine, and cyanocobalamin decreased the risk of developing age-related macular degeneration by 34.7%. The amount of folic acid used in this clinical trial – 2500 μg – was higher than the Tolerable Upper Intake Level of 1000 μg.

Folic acid, B12 and iron

There is a complex interaction between folic acid, vitamin B12 and iron. A deficiency of one may be "masked" by excess of another so the three must always be in balance.

Toxicity

The risk of toxicity from folic acid is low, because folate is a water-soluble vitamin and is regularly removed from the body through urine. One potential issue associated with high dosages of folic acid is that it has a masking effect on the diagnosis of pernicious anaemia (vitamin B12 deficiency), and a variety of concerns of potential negative impacts on health.

Folate deficiency

Main article: Folate deficiency

Folate deficiency can be caused by unhealthy diets that do not include enough fruits and vegetables, diseases in which folic acid is not well absorbed in the digestive system (such as Crohn's disease or celiac disease), some genetic disorders that affect levels of folate, and certain medicines (such as phenytoin, sulfasalazine, or trimethoprim-sulfamethoxazole). Folate deficiency is accelerated by alcohol consumption.
Folate deficiency may lead to glossitis, diarrhea, depression, confusion, anemia, and fetal neural tube defects and brain defects (during pregnancy). Other symptoms include fatigue, gray hair, mouth sores, poor growth, and swollen tongue. Folate deficiency is diagnosed by analyzing CBC and plasma vitamin B12 and folate levels. CBC may indicate megaloblastic anemia but this could also be a sign of vitamin B12 deficiency. A serum folate of 3 μg/L or lower indicates deficiency. Serum folate level reflects folate status but erythrocyte folate level better reflects tissue stores after intake. Serum folate reacts more rapidly to folate intake than erythrocyte folate. An erythrocyte folate level of 140 μg/L or lower indicates inadequate folate status. Increased homocysteine level suggests tissue folate deficiency but homocysteine is also affected by vitamin B12 and vitamin B6, renal function, and genetics. 

One way to differentiate between folate deficiency from vitamin B12 deficiency is by testing for methylmalonic acid levels. Normal MMA levels indicate folate deficiency and elevated MMA levels indicate vitamin B12 deficiency. Folate deficiency is treated with supplemental oral folate of 400 to 1000 μg per day. This treatment is very successful in replenishing tissues, even if deficiency was caused by malabsorption. Patients with megaloblastic anemia need to be tested for vitamin B12 deficiency before folate treatment, because if the patient has vitamin B12 deficiency, folate supplementation can remove the anemia, but can also worsen neurologic problems. Morbidly obese patients with BMIs of greater than 50 are more likely to develop folate deficiency. Patients with celiac disease have a higher chance of developing folate deficiency. Cobalamin deficiency may lead to folate deficiency, which, in turn, increases homocysteine levels and may result in the development of cardiovascular disease or birth defects.

### Malaria

Some studies show iron–folic acid supplementation in children under 5 may result in increased mortality due to malaria; this has prompted the World Health Organization to alter their iron–folic acid supplementation policies for children in malaria-prone areas, such as India.

### Dietary reference intake

Because of the difference in bioavailability between supplemented folic acid and the different forms of folate found in food, the dietary folate equivalent (DFE) system was established. One DFE is defined as 1 μg of dietary folate, or 0.6 μg of folic acid supplement.

<table>
<thead>
<tr>
<th>Age</th>
<th>Infants (AI)</th>
<th>Infants (UL)</th>
<th>Adults (RDA)</th>
<th>Adults (UL)</th>
<th>Pregnant women (RDA)</th>
<th>Pregnant women (UL)</th>
<th>Lactating women (RDA)</th>
<th>Lactating women (UL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 months</td>
<td>65</td>
<td>None set</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7–12 months</td>
<td>80</td>
<td>None set</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age Group</td>
<td>EARs</td>
<td>RDA</td>
<td>Adequate Intake</td>
<td>UL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>-----</td>
<td>-----------------</td>
<td>----</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 years</td>
<td>150</td>
<td>300</td>
<td>300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–8 years</td>
<td>200</td>
<td>400</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–13 years</td>
<td>300</td>
<td>600</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–18</td>
<td>400</td>
<td>800</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19+</td>
<td>400</td>
<td>1000</td>
<td>800</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Dietary Reference Intakes (DRIs) were developed by the United States National Academy of Sciences to set reference values for planning and assessing nutrient intake for healthy people. DRIs incorporate four reference values: Estimated Average Requirements (EARs), Recommended Dietary Allowances (RDAs; the daily intake level that is adequate for 97–98% of the population in the United States), Adequate Intakes, for when the existing science is inadequate to set EARs and RDAs, and tolerable upper intake levels (UL, the highest level of intake considered safe). The UL for folate refers to only synthetic folic acid, as no health risks have been associated with high intake of folate from food sources. The European Food Safety Authority reviewed the same safety question and also set the adult UL at 1000 μg.

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For folic acid labeling purposes 100% of the Daily Value was 400 μg. As of the May 2016 update it was kept unchanged at 400 μg. A table of the pre-change adult Daily Values is provided at Reference Daily Intake. Food and supplement companies have until 28 July 2018 to comply with the change.

**Sources**

Vitamins C and M as featured on a monument in front of University of Warsaw's Centre of New Technologies

Folate naturally occurs in a wide variety of foods, including vegetables (particularly dark green leafy vegetables), fruits and fruit juices, nuts, beans, peas, dairy products, poultry and meat, eggs, seafood, grains, and some beers. Avocado, beetroot, spinach, liver, yeast, asparagus, and Brussels sprouts are among the foods with the highest levels of folate.
Folic acid is added to grain products in many countries, and in these countries, fortified products make up a significant source of the population's folic acid intake. Because of the difference in bioavailability between supplemented folic acid and the different forms of folate found in food, the dietary folate equivalent (DFE) system was established. 1 DFE is defined as 1 µg of dietary folate, or 0.6 µg of folic acid supplement. This is reduced to 0.5 µg of folic acid if the supplement is taken on an empty stomach.

Folate naturally found in food is susceptible to high heat and ultraviolet light, and is soluble in water. It is heat-labile in acidic environments and may also be subject to oxidation.

Some meal replacement products do not meet the folate requirements as specified by the RDAs.

Folate (B9) can also be processed from the provitamin Pteroylmonoglutamic acid (Vitamin B10).

---

### History

In the 1920s, scientists believed folate deficiency and anemia were the same condition. In 1931, researcher Lucy Wills made a key observation that led to the identification of folate as the nutrient required to prevent anemia during pregnancy. Wills demonstrated that anemia could be reversed with brewer's yeast. In the late 1930s, folate was identified as the corrective substance in brewer's yeast.

It was first isolated via extraction from spinach leaves by Herschel K. Mitchell, Esmond E. Snell, and Roger J. Williams in 1941. Bob Stokstad isolated the pure crystalline form in 1943, and was able to determine its chemical structure while working at the Lederle Laboratories of the American Cyanamid Company. This historical research project, of obtaining folic acid in a pure crystalline form in 1945, was done by the team called the "folic acid boys," under the supervision and guidance of Director of Research Dr. Yellapragada Subbarow, at the Lederle Lab, Pearl River, NY.

This research subsequently led to the synthesis of the antifolate aminopterin, the first-ever anticancer drug, the clinical efficacy was proven by Sidney Farber in 1948. In the 1950s and 1960s, scientists began to discover the biochemical mechanisms of action for folate. In 1960, experts first linked folate deficiency to neural tube defects. In the late 1990s, US scientists realized, despite the availability of folate in foods and in supplements, there was still a challenge for people to meet their daily folate requirements, which is when the US implemented the folate fortification program.

---

### Biological roles
DNA and cell division

A diagram of the chemical structure of folate

Folate is necessary for the production and maintenance of new cells, for DNA synthesis and RNA synthesis through methylation, and for preventing changes to DNA, and, thus, for preventing cancer. It is especially important during periods of frequent cell division and growth, such as infancy and pregnancy. Folate is needed to carry one-carbon groups for methylation reactions and nucleic acid synthesis (the most notable one being thymine, but also purine bases). Thus, folate deficiency hinders DNA synthesis and cell division, affecting hematopoietic cells and neoplasms the most because of their greater frequency of cell division. RNA transcription, and subsequent protein synthesis, are less affected by folate deficiency, as the mRNA can be recycled and used again (as opposed to DNA synthesis, where a new genomic copy must be created). Since folate deficiency limits cell division, erythropoiesis, production of red blood cells, is hindered and leads to megaloblastic anemia, which is characterized by large immature red blood cells. This pathology results from persistently thwarted attempts at normal DNA replication, DNA repair, and cell division, and produces abnormally large red cells called megaloblasts (and hypersegmented neutrophils) with abundant cytoplasm capable of RNA and protein synthesis, but with clumping and fragmentation of nuclear chromatin. Some of these large cells, although immature (reticulocytes), are released early from the marrow in an attempt to compensate for the anemia. Both adults and children need folate to make normal red and white blood cells and prevent anemia. Deficiency of folate in pregnant women has been implicated in neural tube defects (NTD); therefore, many developed countries have implemented mandatory folic acid fortification in cereals, etc. NTDs occur early in pregnancy (first month), therefore women must have abundant folate upon conception. Folate is required to make red blood cells and white blood cells and folate deficiency may lead to anemia, which causes fatigue, weakness and inability to concentrate.

DNA and amino acid production

Metabolism of folic acid to recycle homocysteine into methionine

In the form of a series of tetrahydrofolate (THF) compounds, folate derivatives are substrates in a number of single-carbon-transfer reactions, and also are involved in the synthesis of dTMP (2′-deoxythymidine-5′-phosphate) from dUMP.
(2'-deoxyuridine-5'-phosphate). It is a substrate for an important reaction that involves vitamin B₁₂ and it is necessary for the synthesis of DNA, and so required for all dividing cells.⁸²

The pathway leading to the formation of tetrahydrofolate (FH₄) begins when folic acid (F) is reduced to dihydrofolate (DHF) (FH₂), which is then reduced to THF. Dihydrofolate reductase catalyses the last step.⁸³ Vitamin B₃ in the form of NADPH is a necessary cofactor for both steps of the synthesis. Thus, hydride molecules are transferred from NADPH to the C6 position of the pteridine ring to reduce folic acid to THF.⁸⁴

Methylene-THF (CH₂FH₄) is formed from THF by the addition of a methylene bridge from one of three carbon donors: formate, serine, or glycine. Methyl tetrahydrofolate (CH₃-THF, or methyl-THF) can be made from methylene-THF by reduction of the methylene group with NADPH.

Another form of THF, 10-formyl-THF, results from oxidation of methylene-THF or is formed from formate donating formyl group to THF. Also, histidine can donate a single carbon to THF to form methenyl-THF.

Vitamin B₁₂ is the only acceptor of methyl-THF, and this reaction produces methyl-B₁₂ (methylcobalamin). There is also only one acceptor for methyl-B₁₂, homocysteine, in a reaction catalyzed by homocysteine methyltransferase. These reactions are important because a defect in homocysteine methyltransferase or a deficiency of B₁₂ may lead to a so-called "methyl-trap" of THF, in which THF converts to a reservoir of methyl-THF. Thereafter, this THF has no way of being metabolized, and serves as a sink of THF that causes a subsequent deficiency in folate.⁷⁶ Thus, a deficiency in B₁₂ can generate a large pool of methyl-THF that is unable to undergo reactions and mimics folate deficiency.

The reactions that lead to the methyl-THF reservoir can be shown in chain form:

folate → dihydrofolate → tetrahydrofolate ↔ methylene-THF → methyl-THF

Folate metabolism
Conversion to biologically active derivatives

All the biological functions of folic acid are performed by tetrahydrofolate and other derivatives. Their biological availability to the body depends upon dihydrofolate reductase action in the liver. This action is unusually slow in humans, being less than 2% of that in rats (and with an almost-5-fold variation in enzymatic activity), leading to the accumulation of unmetabolized folic acid.[85] It has been suggested this low activity limits the conversion of folic acid into its biologically active forms "when folic acid is consumed at levels higher than the Tolerable Upper Intake Level (1 mg/d for adults)."[85]

Overview of drugs that interfere with folate reactions

A number of drugs interfere with the biosynthesis of folic acid and THF. Among them are the dihydrofolate reductase inhibitors such as trimethoprim, pyrimethamine, and methotrexate; the sulfonamides (competitive inhibitors of 4-aminobenzoic acid in the reactions of dihydropteroate synthetase).

Valproic acid, one of the most commonly prescribed anticonvulsants that is also used to treat certain psychological conditions, is a known inhibitor of folic acid, and as such, has been shown to cause neural tube defects and cases of spina bifida and cognitive impairment in the newborn. Because of this considerable risk, those mothers who must continue to use valproic acid or its derivatives during pregnancy to control their condition (as opposed to stopping the drug or switching to another drug or to a lesser dose) should take folic acid supplements under the direction and guidance of their health care providers.

The National Health and Nutrition Examination Survey (NHANES III 1988–91) and the Continuing Survey of Food Intakes by Individuals (1994–96 CSFII) indicated most adults did not consume adequate folate.[86] However, the folic acid fortification program in the United States has increased folic acid content of commonly eaten foods such as cereals and grains, and as a result, diets of most adults now provide recommended amounts of folate equivalents.[88]
In the USA many grain products are fortified with folic acid.

See also: Food fortification

**Folic acid fortification** is a process where folic acid is added to flour with the intention of promoting public health through increasing blood folate levels in the populace. In the USA, food is fortified with folic acid, only one of the many naturally occurring forms of folate, and a substance contributing only a minor amount to the folates in natural foods.\(^{[57]}\)

Since the discovery of the link between insufficient folic acid and neural tube defects, governments and health organizations worldwide have made recommendations concerning folic acid supplementation for women intending to become pregnant.\(^{[57]}\)

Fortification is controversial, with issues having been raised concerning individual liberty,\(^{[57]}\) as well as the health concerns described in the **Toxicity** section above. In the USA, there is concern that the federal government mandates fortification, but does not provide monitoring of potential undesirable effects of fortification.\(^{[57]}\)

76 countries worldwide require mandatory folic acid fortification of at least one major cereal grain, with nearly all fortifying at least wheat flour, according to November 2013 data from the Flour Fortification Initiative.\(^{[89]}\) These countries are:

Antigua and Barbuda, Argentina, Australia, Bahamas, Bahrain, Barbados, Belize, Benin, Bolivia (Plurinational State of), Brazil, Burkina Faso, Cameroon, Canada, Chile, Colombia, Costa Rica, Cote d'Ivoire, Cuba, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Fiji, Ghana, Grenada, Guatemala, Guinea, Guyana, Haiti, Honduras, Indonesia, Iran (Islamic Republic of), Iraq, Jamaica, Jordan, Kazakhstan, Kenya, Kosovo, Kuwait, Kyrgyzstan, Liberia, Mali, Mauritania, Mexico, Morocco, Nepal, Nicaragua, Niger, Nigeria, Oman, Palestine (Occupied Territory), Panama, Papua New Guinea, Paraguay, Peru, Republic of Moldova, Rwanda, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Saudi Arabia, Senegal, Sierra Leone, Solomon Islands, South Africa, Suriname, Tanzania
As of November 2013, no EU country has mandated folic acid fortification.\[^{89}\]

### Australia

There has been previous debate in Australia regarding the inclusion of folic acid in products such as bread and flour.\[^{90}\]

Australia and New Zealand have jointly agreed to fortification though the Food Standards Australia New Zealand. Australia will fortify all flour from 18 September 2009.\[^{91}\] Although the food standard covers both Australia and New Zealand, an Australian government official has stated it is up to New Zealand to decide whether to implement it there, and they will watch with interest.\[^{92}\]

The requirement is 0.135 mg of folate per 100g of bread.

### Canada

In 2003, a Hospital for Sick Children, University of Toronto research group published findings showing the fortification of flour with folic acid in Canada has resulted in a dramatic decrease in neuroblastoma, an early and very dangerous cancer in young children.\[^{93}\] In 2009, further evidence from McGill University showed a 6.2% decrease per year in the birth prevalence of severe congenital heart defects.\[^{94}\]

Folic acid used in fortified foods is a synthetic form called pteroylmonoglutamate.\[^{95}\] It is in its oxidized state and contains only one conjugated glutamate residue.\[^{96}\] Folic acid therefore enters via a different carrier system from naturally occurring folate, and this may have different effects on folate binding proteins and its transporters.\[^{96}\] Folic acid has a higher bioavailability than natural folates and are rapidly absorbed across the intestine,\[^{95}\] therefore it is important to consider the Dietary Folate Equivalent (DFE) when calculating one's intake. Natural occurring folate is equal to 1 DFE, however 0.6 µg of folic acid is equal to 1 DFE.

Folic acid food fortification became mandatory in Canada in 1998, with the fortification of 150 µg of folic acid per 100 grams of enriched flour and uncooked cereal grains.\[^{97}\] The purpose of fortification was to decrease the risk of neural tube defects in newborns.\[^{97}\] It is important to fortify grains because it is a widely eaten food and the neural tube closes in the first four weeks of gestation, often before many women even know they are pregnant. Canada's fortification program has been successful with a decrease of neural tube defects by 19% since its introduction.\[^{98}\] A seven-province study from 1993 to 2002 showed a reduction of 46% in the overall rate of neural tube defects after folic acid fortification was introduced in Canada.\[^{99}\] The fortification program was estimated to raise a person's folic acid intake level by 70–130 µg/day, however an increase of almost double that amount was actually observed.\[^{98}\] This could be from the fact that many foods are over fortified by 160–175% the predicted value.\[^{98}\] In addition, much of the elder population take supplements that adds 400 µg to their daily folic acid intake. This is a concern because 70–80% of the population have detectable
levels of unmetabolized folic acid in their blood and high intakes can accelerate the growth of preneoplastic lesions. [100] It is still unknown the amount of folic acid supplementation that might cause harm. [97]

**Supplementation promotion**

According to a Canadian survey, 58% of women said they took a folic acid containing multivitamin or a folic acid supplement as early as three months before becoming pregnant. Women in higher income households and with more years of school education are using more folic acid supplements before pregnancy. Women with planned pregnancies and who are over the age of 25 are more likely to use folic acid supplement. Canadian public health efforts are focused on promoting awareness of the importance of folic acid supplementation for all women of childbearing age and decreasing socio-economic inequalities by providing practical folic acid support to vulnerable groups of women. [99]

**New Zealand**

New Zealand was planning to fortify bread (excluding organic and unleavened varieties) from 18 September 2009, but has opted to wait until more research is done. [91]

The Association of Bakers [101] and the Green Party [102] have opposed mandatory fortification, describing it as "mass medication". Food Safety Minister Kate Wilkinson reviewed the decision to fortify in July 2009, citing links between overconsumption of folate with cancer. [103] The New Zealand Government is reviewing whether it will continue with the mandatory introduction of folic acid to bread. [104]

**United Kingdom**

There has been previous debate in the United Kingdom regarding the inclusion of folic acid in products such as bread and flour. [105] While the Food Standards Agency has recommended folic acid fortification, [106][107][108] and wheat flour is fortified with iron, [89] folic acid fortification of wheat flour is allowed voluntarily rather than required.

**United States**

The United States Public Health Service recommends an extra 0.4 mg/day for newly pregnant women, which they can take as a pill. However, many researchers believe this supplementation can never work effectively enough, since about half of all pregnancies in the U.S. are unplanned, and not all women comply with the recommendation. Approximately 53% of the US population uses dietary supplements and 35% uses dietary supplements that contain folic acid. [109]

Men consume more folate (in dietary folate equivalents) than women, and non-Hispanic whites have higher folate intakes than Mexican Americans and non-Hispanic blacks. [109] Twenty-nine percent of black women have inadequate intakes of folate. [109] The age group consuming the most folate and folic acid is the >50 group. [109] 5% of the population exceeds the Tolerable Upper Intake Level. [109]

In 1996, the United States 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. [110][111] This ruling took effect on
1 January 1998, and was specifically targeted to reduce the risk of neural tube birth defects in newborns. There are concerns that the amount of folate added is insufficient. In October 2006, the Australian press claimed that U.S. regulations requiring fortification of grain products were being interpreted as disallowing fortification in non-grain products, specifically Vegemite (an Australian yeast extract containing folate). The FDA later said the report was inaccurate, and no ban or other action was being taken against Vegemite.

As a result of the folic acid fortification program, fortified foods have become a major source of folic acid in the American diet. The Centers for Disease Control and Prevention in Atlanta, Georgia used data from 23 birth defect registries covering about half of United States births, and extrapolated their findings to the rest of the country. These data indicate that, since the addition of folic acid in grain-based foods as mandated by the FDA, the rate of neural tube defects dropped by 25% in the United States. Before folic acid fortification, about 4,100 pregnancies were affected by a neural tube defect each year in the United States. After fortification, this number declined to around 3,000. The results of folic acid fortification on the rate of neural tube defects in Canada have also been positive, showing a 46% reduction in prevalence of NTDs; the magnitude of reduction was proportional to the prefortification rate of NTDs, essentially removing geographical variations in rates of NTDs seen in Canada before fortification.

When the U.S. Food and Drug Administration set the folic acid fortification regulation in 1996, the projected increase in folic acid intake was 100 µg/d. Data from a study with 1480 subjects showed that folic acid intake increased by 190 µg/d and total folate intake increased by 323 µg dietary folate equivalents (DFE)/d. Folic acid intake above the upper tolerable intake level (1000 µg folic acid/d) increased only among those individuals consuming folic acid supplements as well as folic acid found in fortified grain products. Taken together, folic acid fortification has led to a bigger increase in folic acid intake than first projected.