7.3G: 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 folic acid 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.[8] 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 intake.
dietary intake.[13] 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).[8]

Folic acid was discovered between 1931 and 1943.[14] It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[15] The wholesale cost of supplements in the developing world is between 0.001 and 0.005 USD per dose as of 2014.[16] The term "folic" is from the Latin word folium, which means leaf. Folates occur naturally in many foods especially dark green leafy vegetables and liver.[8]

**Pregnancy and Fertility**

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.

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, Stroke and Cancer**

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.

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. 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. Asian populations had greater protection against stroke with folate supplementation than did European or North American subjects.

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.

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) may increase the risk of colorectal, breast, ovarian, pancreas, brain, lung, cervical, and prostate cancers. Other studies showed that excessive dietary supplementation with synthetic folate may increase the risk of certain cancers, in particular prostate. A 2017 review found no relationship between taking folate supplements and cancer risk.
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.

National Institutes of Health (US) nutritional requirements[65] (μg DFE per day)

<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>
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</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>1–3 years</td>
<td>–</td>
<td>–</td>
<td>150</td>
<td>300</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>4–8 years</td>
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<td>–</td>
<td>200</td>
<td>400</td>
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<td>9–13 years</td>
<td>–</td>
<td>–</td>
<td>300</td>
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<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
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<td>800</td>
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<tr>
<td>19+</td>
<td>–</td>
<td>–</td>
<td>400</td>
<td>1000</td>
<td>600</td>
<td>1000</td>
<td>500</td>
<td>1000</td>
</tr>
</tbody>
</table>

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.

Dietary Sources

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. bFolate 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.
**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. 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.

Fortification is controversial, with issues having been raised concerning individual liberty, 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. 76 countries worldwide (including the USA) 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.

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**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 B$_{12}$ and folate levels. CBC may indicate megaloblastic anemia but this could also be a sign of vitamin B$_{12}$ 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 B$_{12}$ and vitamin B$_{6}$, renal function, and genetics.

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**Contributors**

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