Folate

The Untold Story

Grains they're essential! Les produits céréaliers, essentiels pour la santé !

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In summary

Folate is an essential B-vitamin, required in the production of new cells and is especially important for neonatal development.

Mandatory fortification of white wheat flour, enriched pasta and enriched cornmeal with folic acid came into effect in 1998. Since then a number of positive results have been observed from the increased intake of folic acid including:

- Improved folate status in Canadian women;
- Approximately 50% reduction in neural tube defects across Canada;
- A reduction in serum homocysteine levels, an indicator of cardiovascular disease risk;
- A reduction in neuroblastoma, a tumor seen in infants.

Encouraging consumption of legumes, dark green vegetables, enriched pasta and products made from white wheat flour will help ensure adequate folate intake in the Canadian population.

In 1996 Canada's food industry agreed with Health Canada to the voluntary addition of folic acid to white wheat flour, enriched pasta and enriched cornmeal as a public health measure to reduce the incidence of neural tube defects. Folic acid fortification of these food ingredients became mandatory in 1998. What impact has this measure had on health?

In an attempt to answer this question, this paper will address:

- Folate metabolism
- Folic acid fortification in Canada
- Benefits of fortification
- Risks of fortification
- Food folate and folic acid intake
- Ways to help consumers

Fast facts about folate

Folate is the umbrella term used interchangeably with the terms folic acid and folacin. Folate comes in two forms.

1) **naturally occurring in food.** Food folate is in a bound form and the body only absorbs about 50%. Primary sources are legumes, green leafy vegetables, some fruits and wheat germ.

2) **synthetic folate**, often referred to as folic acid, has an absorption rate of 85-100%. This is the form in supplements and in fortified food.

To address the difference in absorption rates, folate values are determined by

Dietary Folate Equivalents

1µg food folate = 1 µg DFE

1µg folic acid (from fortified food) = 1.7 µg DFE[1]

Folate Metabolism

Folate is a water-soluble B-vitamin sometimes referred to as vitamin B_9. Folate is essential for making new cells. The cells of the GI tract and the blood turn over rapidly and are most vulnerable to folate deficiency. Folate is critical during periods of rapid tissue growth such as in pregnancy and is especially important in early fetal development.

Folate functions in several key biological processes including:

- DNA synthesis,
- Purine synthesis,
- Generation and utilization of formate, and
- Amino acid conversions such as homocysteine to methionine.[1]

Folate deficiency can be detected by measuring a decrease in serum folate and red blood cell folate and an increase in homocysteine concentration. The studies of women who have given birth to children with neural tube defects (NTDs) show higher homocysteine levels when compared to women who have given birth to normal children. Folate's role in the prevention of neural tube defects and its role in the prevention of chronic diseases are areas of intense study.

Folic Acid Fortification in Canada

History

Three percent of all newborns in Canada are born with birth defects. Neural tube defects are a type of birth defect, of which the most common forms are spina bifida and anencephaly. NTDs occur 7.5 times in 10,000 births, although this rate does not include the number of pregnancies that are terminated.[2]

In the past, researchers observed that the rates of NTDs increased during times of drought, famine and war, when diet was severely compromised. Clearly, a healthy diet reduces risk of NTDs. Intervention studies later demonstrated that adequate folate/folic acid intake could reduce the incidence of NTDs by up to 70%.[2]

The timing of folic acid intake is central to its effectiveness. To reduce risk of NTDs, adequate folic acid is required periconceptionally—2-3 months before conception and continued through the first trimester. Early in the 1990's the Canadian government and health professional organizations launched extensive education programs advising women of child bearing age to take a 0.4 mg folic acid supplement each day. Unfortunately, even the most aggressive public health campaigns failed to increase supplement use.[3] The majority of women during their reproductive years and specifically those who get pregnant do not consume folic acid supplements.[3,4,5]

Mandatory Fortification

Health Canada uses food fortification as the way to correct or prevent nutritional problems of public health significance.[6]

In 1996 optional folate fortification occurred at levels of 0.15 mg/100 g for white wheat flour and 0.27 mg/100 g for enriched pasta. These levels became mandatory in November 1998[7] because not enough women took folic acid supplements prior to pregnancy or early enough in their pregnancy to observe a decrease in NTDs. In addition, in January 1998, the United States made folic acid fortification mandatory; matching the fortification levels to the US allowed no disruption in trade with our neighbour.[8]

In Canada, folic acid fortification is mandatory for:

- white wheat flour,
- enriched pasta, and
- enriched corn meal.

Table 1 lists all the products that can potentially be fortified with folic acid.[9]

Table 1 Folate fortification

Mandatory Fortification in Commonly Consumed Foods	Voluntary Fortification in Commonly Consumed Foods
• Enriched alimentary pastes (pasta) • White wheat flour • Enriched corn meal	• Breakfast cereals • Fruit-flavoured drinks • Bases, concentrates and mixes that are used for making fruit-flavoured drinks • Alimentary pastes (pasta) • Corn meal • Pre-cooked rice • Beverages derived from legumes, nuts, cereal grains or potatoes to which a vitamin or mineral has been added
Mandatory Fortification in Specialty Foods	**Voluntary Fortification in Specialty Foods**
• Infant formulas and formulated liquid diets • Food represented for use in a very low-energy diet • Simulated meat products, simulated poultry meat products, meat product extenders and poultry product extenders • Meal replacements and nutritional supplements • Products simulating whole egg	• Evaporated goat's milk • Evaporated partly skimmed and skimmed goat's milk • Fluid or dried whole, skimmed or partly skimmed goat's milk

Benefits of Folic Acid Fortification

Folate Intake and Status

Nutrient intake surveys conducted after mandatory fortification reveal improved dietary folate intakes, with 86% of women meeting the Estimated Average Requirement (EAR) of 320 µg/day, compared to only 36% prior to fortification.[10] Intakes of folate increased from 296 to 470 µg/day in British Columbian women and from 262 to 318 µg/day in Newfoundland women after fortification.[10,11]

The US data showed similar gains for women. Folate intakes increased from 238 µg in 1988-94 to 327 µg in 1999-2000 based on data from NHANES.[12]

In addition, both mean serum folate levels and mean red blood cell folate levels have increased since fortification. The prevalence of folate insufficiency (serum folate < 3.4 nmol/L and RBC folate <215 nmol/L) decreased between 59 and 77% after fortification.[13] The US experienced an even more dramatic improvement. The rate of low serum folate levels in women ages 12-49 years decreased from a prevalence of 20% to 0.8%.[14] Table 2 lists serum and red blood cell folate values.

Table 2 Folate status

Reference	Qualification	Mean serum folate (nmol/L)	Mean RBC folate (nmol/L)
Pfeiffer (14)	Adults and children All subjects 1988-1994 All subjects 1999-2000	 12.0 29.7	 398 636
Ray (13)	Women (Ontario) Pre-fortification During fortification Post fortification	 18.5 27.2 27.1	 680.3 804.1 851.6
Liu (11)	Women 19-44 years (Newfoundland) Pre-fortification Post fortification	 13.5 18.1	 625 818
Ray (15)	Women of reproductive age Pre-fortification Post-fortification		 527 741

Folic Acid and Neural Tube Defects

Both Canada and the United States have observed a decrease in rates of neural tube defects. In Ontario, two separate studies observed a significant decrease in the incidence of NTDs. The first study compared 1995 rates to 1999 rates and found a 47% decrease.[16] The second study compared prevalence rates before fortification (1994-1997) with rates following fortification (1998-2000) and found a reduction of 38%.[17] Similar, but more striking results were observed in Nova Scotia and Newfoundland, where incidence of NTDs fell by 54% and 78%, respectively, after fortification.[11,18]

In the US, prevalence of spina bifida and anencephaly decreased by 31% and 16% in the year following fortification.[19]

Experts believe that food fortification is responsible for the improvement in incidence of NTDs. In countries where mandatory fortification has not been implemented, rates of NTDs have not decreased regardless of public health efforts to get women to consume supplements.[20]

Folic Acid and Cardiovascular Disease

An elevated blood homocysteine level is a recognized risk factor for vascular disease.[21] Less clear is whether reducing homocysteine levels with additional folate will improve cardiovascular disease risk and mortality. Model estimates of homocysteine level reductions due to flour folic acid fortification project a decrease in myocardial infarction rates by 13% in women and 8% in men.[22]

The Framingham Offspring Study cohort confirmed a decrease in total homocysteine levels post fortification. The prevalence of those identified as having high homocysteine levels (>13 µmol/L) had the most significant reduction from 18.7 to 9.8%.[23] In a group of patients with coronary artery disease the percentage with high homocysteine levels were reduced from 41 to 28 post fortification.[24] There was also a small but not statistically significant decrease in mortality. And in a double-blind, placebo-controlled, randomized trial, cardiovascular patients presenting with impaired flow-mediated dilation, showed improvement in the folic acid group compared to the placebo group.[25]

More research is needed to determine if additional intake of folic acid through fortification or supplements can further reduce homocysteine levels and ultimately reduce cardiovascular disease.

Folic Acid and Cancer

Folic acid is thought to have an impact on cancer risk due to its role in DNA synthesis and repair. Animal studies have shown that folic acid can prevent colorectal cancer in genetically engineered mice.[26]

Results from epidemiological studies are conflicting. Some studies show a relationship between higher folate – both plasma levels and dietary intake levels – and a decrease in colorectal cancer, breast cancer and prostate cancer.[26,27,28] Others show no protective effect.[29] A review concluded that folic acid plays a role in the reduction of colorectal cancer, but that the actual role and mechanism has yet to be determined.[29]

Neuroblastoma, an embryonic tumor, is the second most common pediatric tumor in children. Due to the role of folic acid in the prevention of neural tube defects, a group of Canadian researchers examined whether the incidence rates of this tumor differed post fortification. French and colleagues found a 60% reduction in neuroblastoma after folic acid fortification became mandatory, compared to before fortification. There was no difference in the rates of acute lymphoblastic leukemia or hepatoblastoma, two other pediatric cancers.[30]

The long term effects of folic acid fortification on cancer prevention are still unknown. Further research is needed to determine the exact role of folic acid in cancer prevention.

Folic Acid and Brain Function

Historically, folate deficiency has been associated with mood disturbances and depression. Folic acid given along with antidepressant drugs has been shown to be more effective than the drugs alone.[31]

Elevated homocysteine levels, a measure of folic acid insufficiency has been associated with declining cognitive function. A recent review of population studies concluded that there is evidence that elevated homocysteine levels are related to folate deficiency, cognitive decline and dementia.[32] A 2005 published longitudinal study found that participants with the lowest serum folate levels had the greatest cognitive decline.[33]

Two other longitudinal studies looking at intake data found conflicting results. One observed a decreased rate of Alzheimer's disease with higher folate intake, especially at levels above the RDA.[34] The other study noted a greater cognitive decline in elderly participants who had intakes in the highest quintile, although it was reported that most of these participants were taking multivitamin supplements containing folic acid.[35] The authors speculated that one reason for the unexpected results could be the possibility of a masked vitamin B_{12} deficiency. However, since biochemical markers were not measured in this study, a vitamin B_{12} deficiency could not be determined.

Risks of Folic Acid Fortification

High Intakes

Folate/folic acid is a water soluble vitamin. There is no concern for toxicity and there have been no documented adverse effects from food folate or fortified food consumption. The Tolerable Upper Intake Level (UL), which is the highest amount of a nutrient taken daily that will pose no risk, has been established using data from supplement use. Table 4 lists the UL of folate for different age groups.[1]

Table 3 UL for folate

Age (years)	Daily intake from fortified foods or supplements (µg)
1-3	300
4-8	400
9-13	600
14-18	800
19 and older	1000

Some health professionals are concerned that young children may have intakes of folate above their UL now that mandatory folic acid fortification exists. However, very little data exists on the folate intakes of Canadian children and teens. In 1997-8, the year preceding mandatory fortification, Canadian male teenagers had an intake of 299 µg/day while Canadian female teenagers (13-17 years) consumed 274 µg/day.[36]

In two provinces where the contribution of folic acid from fortified foods was measured in women, total intake increased by 70 – 104 µg/day.[10,11] The intake of an additional 100 µg/day of folic acid from fortified foods, without supplements, does not come close to the current UL.

Masking Vitamin B_{12} deficiency in the Elderly

Both folate and vitamin B_{12} are involved as coenzymes in the same metabolic pathways. Vitamin B_{12} deficiency or macrocytic anemia is more common in the elderly due to malabsorption of food-bound vitamin B_{12} and in lacto-ovo vegetarians due to lack of meat consumption. The hematologic measurements associated with macrocytic anemia often disappear with folic acid treatment. Although symptoms may disappear, there is concern that the underlying deficiency remains, thereby "masking" the diagnosis.[21] Uncorrected vitamin B_{12} deficiency can lead to neurological damage and memory loss.

Both a Canadian and US study that compared the rate of low serum vitamin B_{12} levels in an elderly population before and after fortification, found that although the rate increased, it remained below 1%.[14,15] In the Newfoundland study, serum vitamin B_{12} increased after fortification in both women 19-44 years of age and in seniors over the age of 65 years.[11]

For people consuming folic acid supplements above the UL, it is recommended that the supplement include vitamin B_{12} and that their vitamin B_{12} status be monitored.[2]

Food Folate and Folic Acid Intake

Dietary Folate Equivalents

Individuals consume a mix of naturally occurring *food folate* as well as foods fortified with *synthetic folic acid*. The absorption of food folate differs from folic acid. Folic acid consumed as a supplement on an empty stomach is 100% absorbed. When taken with food, folic acid from fortified foods or from supplements has an 85% absorption rate. Food folate is only 50% absorbed. As a result, both recommendations and food composition tables provide the folate value in Dietary Folate Equivalents (DFE).[1]

1 µg food folate = 1 µg DFE
1 µg folic acid (from fortified food) = 1.7 µg DFE

Recommendations

Dietary Reference Intakes for folate consist of three values:

- Recommended Dietary Allowance (RDA) – the average daily dietary intake level sufficient to meet the needs of 97.5% of the healthy individuals; intended as a goal for daily intake by individuals (Table 4);
- Estimated Average Requirement (EAR) – the daily intake value estimated to meet the needs of half the healthy individuals; used to determine prevalence of inadequate intake of a group;
- Tolerable Upper Intake Level – the highest level of daily intake that is likely to pose no risk of adverse health effects (discussed above).

Table 4 RDA for folate

Life Stage (age in years in both genders)	µg/day (as DFE)	Life Stage (age in years in females)	µg/day (as DFE)
1-3	150	Pregnancy ≤18-50	600
4-8	200		
9-13	300	Lactation ≤18-50	500
14->70	400		

The RDA for folate is listed as Dietary Folate Equivalents (DFE) because it is expected that dietary sources include food folate and folic acid from fortified foods. For pregnant women the recommendation is that 400 µg/day be in the form of folic acid from supplements or fortified foods in addition to consuming 200 µg/day from food folate.[1] Since 75% of women are still not consuming the recommendation for reproductive years,[10] some researchers suggest that more products be fortified with folic acid (e.g. whole wheat flour) or with higher levels.[37]

Food Guide

Excellent sources of folate (>55 µg) come from three food groups in Canada's Food Guide to Healthy Eating:

1. Grain Products (enriched pasta, and products made with white wheat flour)
2. Vegetables and Fruit (dark green vegetables such as spinach, asparagus, broccoli, and romaine lettuce and fruits such as orange juice and avocado)
3. Meat and Alternatives (most legumes, sunflower seeds)

Directional statements in the Food Guide aid consumers in the selection of a folate-rich diet.

"Choose whole grain and **enriched products** more often."

"Choose **dark green…vegetables and orange fruit** more often."

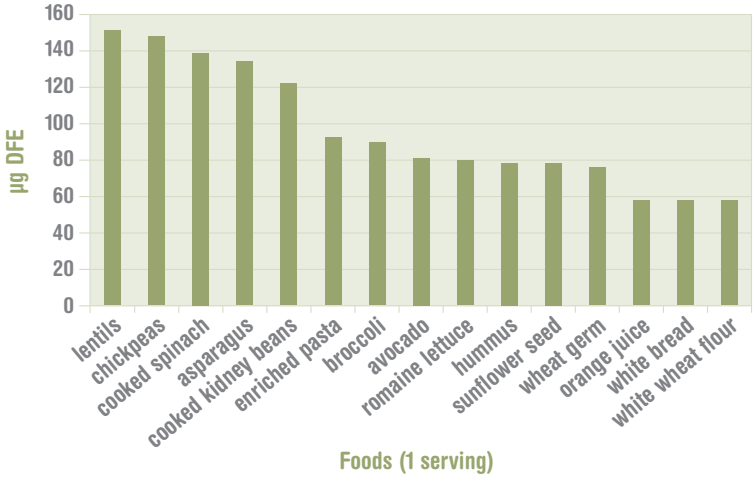
"Choose…**dried peas, beans and lentils** more often."

Ways to help consumers

Consumers can be reminded of the benefits of folic acid fortification on folate status and on health in general and be encouraged to:

- choose fortified products such as white wheat flour, enriched pasta and enriched cornmeal and products made with fortified flour such as bread and rolls;
- select whole grain and enriched breads and pasta everyday and get the benefits of both;
- include excellent folate sources such as legumes, dark green vegetables and orange juice;
- try doubling up their folate intake with food combinations such as
  - pasta with broccoli or asparagus,
  - kidney bean chili with pasta,
  - a variety of breads with hummus, guacomole or peanut butter,
  - lasagna with spinach;
- take a multivitamin supplement with folic acid if they are planning to get pregnant.

Excellent Sources of Folate



Values obtained from the Canadian Nutrient File 2005 online search at **http://www.hc-sc.gc.ca/fn-an/nutrition/fiche-nutri-data/index_e.html**[38]

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