Global Experiences and Evidence For Fortifying with Folic Acid

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Enhancing Grains for Healthier Lives

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Introduction to fortification

Fortification as discussed in this overview refers to adding essential vitamins and minerals (sometime called micronutrients) to staple foods such as wheat flour, rice, salt, and oil. The Food Fortification Initiative (FFI) is a network of public, private, and civic sector partners with a collective goal of preventing micronutrient deficiencies through the mandatory fortification of industrially milled cereal grains (wheat flour, maize flour, rice). FFI monitors the global status of cereal grain fortification and provides technical support internationally to ministries of health and development partners to plan, implement, and monitor cereal grain fortification.

Although multiple nutrients can be added in fortification, this brief focuses on global experience and scientific literature of including folic acid in wheat flour and rice fortification. This intervention helps prevent serious birth defects of the brain and spine known as neural tube defects or NTDs.

Quality of scientific evidence

Scientific evidence is presented for mandatory fortification with folic acid or supplementation with folic acid. Scientific studies are not all of equal quality; when interpreting evidence, it is important to understand whether a study is able to identify causation (cause and effect) or association (link, correlation, relationship). Temporal data or associations do not indicate cause-effect. Where available, this brief refers to meta-analyses or reviews to summarize the evidence for a health outcome.

Background

Global folic acid fortification practices

As of December 2016, 86 countries have legislation that requires fortification of at least one cereal grain. Wheat flour is the most commonly fortified cereal grain, followed by maize flour and then rice (Table 1).

Table 1: Number of countries with mandated fortification legislation, by cereal grain[1]

	Wheat flour only	Wheat flour, Maize flour	Wheat flour, Rice	Wheat flour, Maize flour, Rice	Rice only	Total
# of countries	66	14	3	2	1	86

The fortification standards for 80 of these countries require folic acid in wheat flour, maize flour, or rice (Table 2). The list of countries by nutrients required is in the Appendix (Table 5 and Table 6).

Table 2: Number of countries with mandated fortification legislation that require folic acid, by cereal grain[2]

	Wheat flour only	Wheat flour, maize flour	Wheat flour, Rice	Wheat flour, Maize flour, Rice	Rice only	Total
# of countries	61	14	2	2	0	80

Fortification of wheat flour was first legislated in the United States 1942 to include thiamin, niacin, riboflavin, and iron[3]. Randomized controlled trials in the 1990s proved that folic acid prevents most neural

[1] Food Fortification Initiative. Global Progress, 2016. Available at: http://ffinetwork.org/global_progress/index.php.
[2] Food Fortification Initiative Database, 2016. Individual country profiles with fortification standards available at: http://ffinetwork.org/country_profiles/index.php. Aggregated database available upon request: info@ffinetwork.org.
[3] Bendich A, et al. Eds. Part IV: Nutrition Transitions Around the World. In: Preventive Nutrition: The Comprehensive Guide for Health Professionals. Edition 4. Springer Science & Business Media, 2009.

tube defects. In 1996 Oman became the first country to achieve national-scale fortification of wheat flour with folic acid. In 1996 United States and Canada also revised fortification standards to require wheat flour, maize flour, and rice to also include folic acid,[4] with implementation required by 1 January 1998.

In the 20 years since fortification with folic acid began, 80 countries have revised regulations to include folic acid, or passed new fortification legislation that include folic acid.

No country has ever revised standards to remove folic acid as a required nutrient in fortification.

Folate deficiency vs. folate insufficiency

It is important to distinguish between folate *deficiency* and folate *insufficiency* (Table 3). Folate deficiency specifically refers to two conditions: clinical anemia or elevated homocysteine. The World Health Organization (WHO) has identified blood (serum/plasma and red blood cell folate) cut-offs for which either becomes a risk[6]. However, inadequate levels of folate can cause other conditions, most notably for women - increased risk for a pregnancy affected by a NTD. The cut-off for folate insufficiency, at which women are at greater risk for a neural tube defect, is far higher than for folate deficiency. Folate insufficiency can only be assessed as red blood cell folate (from whole blood, not serum or plasma); microbiological assay is recommended (Table 3). For example, clinical deficiency occurs when red blood cell folate levels are <100 ng/mL or 151 ng/mL, whereas the risk of neural tube defects (folate insufficiency) is elevated red blood cell folate levels are <400ng/mL[5]. Studies that only report folate deficiency will not capture the full population of women who are at risk for a pregnancy affected by a neural tube defect.

Inadequate levels of folate have been linked to other conditions (e.g. increased risk for cardiovascular disease) but there are no available blood cut-offs that define this risk.

Table 3: Folate deficiency vs. insufficiency (risk of neural tube defects)[6,7,8]

Indicator	Serum/Plasma Folate (ng/mL)	Red Blood Cell Folate (ng/mL)
Deficiency (clinical anemia)[a]	<3	<100
Deficiency (homocysteine)[a,b]	<6	<275
Insufficiency (risk of NTDs)[c]	N/A	<400

[a] Cut-off values for clinical anemia and folate deficiency based on homocysteine levels are applicable for all age groups.
[b] Cut-off value converted to microbiologic assay equivalence, as published in Pfeiffer CM, et al 2016
[c] Cut-off value for folate insufficiency (risk of NTDs) is only applicable for reproductive age women on a population level

[4] Zimmerman, SL. Fifteen Years of Fortifying With Folic Acid. Sight And Life, Vol. 25 (3), 2011. Available at: http://www.sightandlife.org/fileadmin/data/Magazine/2011/25_3_2011/views_15_years_of_fortifying_with_folic_acid.pdf.
[5] The serum/plasma folate cut-off for folate insufficiency has not been identified.
[6] WHO. Serum and red blood cell folate concentrations for assessing folate status in populations. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2012. Available at: http://apps.who.int/iris/bitstream/10665/75584/1/WHO_NMH_NHD_EPG_12.1_eng.pdf.
[7] WHO. Guideline: optimal serum and red blood cell folate concentrations in women of reproductive age for the prevention of neural tube defects. 2015. Available at: http://www.who.int/nutrition/publications/guidelines/optimalserum_rbc_womenrep_tubedefects/en/.
[8] Pfeiffer CM, et al. Applying inappropriate cutoffs leads to misinterpretation of folate status in the US population. Am J Clin Nutr doi: 10.3945/ajcn.116.138529

Fortification and supplementation: complementary interventions

Supplementation and fortification can work together as complementary interventions, particularly as different stakeholders implement each (fortification by private sector millers, supplementation by the Governments). Fortification will benefit women who do not plan their pregnancies or do not receive or are noncompliant with supplementation recommendations. Fortification will also provide a foundational level of folate for women who do plan their pregnancies. Regardless of fortification status in a country, women are recommended to consume folic acid supplements prior to pregnancy (as is the current recommendation in countries such as the US and Australia, where mandatory fortification programs are in place).

A review of national supplementation recommendations and population practices in several European countries indicated consistently suboptimal impact from supplementation programs[9]. In a review of data from 22 countries, peri-conceptional use of folic acid ranged from 0.5% in Italy to 52% in the Netherlands, despite mass media campaigns[10].

> *Globally few countries have achieved or sustained high coverage of pre-pregnant women with folic acid supplementation, or to document reductions in neural tube defect prevalence as a result.*

Folic acid fortification and relationship to beneficial outcomes: global data

All studies assessing the impact of mandatory fortification programs on health outcomes will be observational studies because everyone in the country receives the intervention and there is no randomization or control group. These studies are supported by smaller scale efficacy studies that established causation. The value of these observational studies is that they demonstrate that a national program in real-life settings can provide similar outcomes as a controlled efficacy study.

Although fortification with folic acid is mandatory in 80 countries, not all countries measure or evaluate health outcomes before and after fortification.

Fortification impact on folate deficiency and insufficiency

In countries with fortification with folic acid, folate deficiency decreases after the implementation of the program (Table 4), in many cases to 1% or below. A review of folate status in Latin American countries has also shown marked decrease in folate deficiency after fortification[11]. Since cut-offs for folate insufficiency are higher than for folate deficiency, folate insufficiency still exists in Canada and the United States despite low folate deficiency. As WHO only announced the folate insufficiency cut-offs in 2015, these countries have not reanalyzed their data or had not collected red blood cell folate.

According to data in these countries, fortification can do much to improve folate status, by eliminating folate deficiency and reducing risk for neural tube defects. But supplements prior to pregnancy will still be an important intervention to ensure women have adequate folate status for optimal prevention of neural tube defects.

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[9] Botto LD, et al (2005) International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? British Medical Journal 330: 571.

[10] Ray JG, et al. (2004) Evidence for suboptimal use of peri-conceptional folic acid supplements globally. British Journal of Obstetrics & Gynaecology 111: 399–408.

[11] Brito A, et al. Folate and Vitamin B12 Status in Latin America and the Caribbean: An Update. Food and Nutrition Bulletin 2015, Vol. 36(Supplement 2) S109-S118.

Table 4: Folate status in countries before and after fortification[12,13,14,15,16]

Country*	Age range	Sample size	Before fortification‡		After fortification‡	
			Folate deficiency	*Folate Insufficiency*	*Folate deficiency*	*Folate insufficiency*
Canada†	6-79 years	5,248	No data	No data	Serum folate: Not measured RBC folate: <1%	RBC folate: 22%
USA	Women 14-44 years	9,958	Serum folate: 24% RBC folate: 3.5%	55-80%[§]	Serum folate: <1% RBC folate: <1%	RBC folate: 22.3%
Fiji†	Women 15-45 years	869	Serum folate: 8.1%	RBC folate: Not measured	Serum folate: 1%	RBC folate: Not measured

‡Cut-offs: Folate deficiency: serum folate <10 nmol/L, RBC folate concentration <305 nmol/L; Folate insufficiency: RBC folate concentration <906 nmol/L

*In North America, flour fortification with folic acid began in 1998; data were collected from 2007-2009 (Canada); 1999-2010 (folate deficiency, before/after fortification) and 2007-2012 (folate insufficiency, after fortification) (USA); In Fiji, flour fortification with folic acid began in 2005; data were collected in 2004 (before fortification) and 2010 (after fortification).

†The WHO cut-offs recommend the use of the microbiologic assay in order for best comparison with the cut-off. Canada and Fiji used immunoassays, which have been shown to vary as much as 30% compared to the microbiologic assay.

[§]Prevalence range depending on race.

Fortification impact on folate deficiency anemia

Nutritional anemia can be caused by deficiencies of multiple nutrients; iron is one of the best known, but deficiencies of zinc, vitamin B12, and folate can also lead to anemia. In the United States, prior to fortification, folate deficiency accounted for 6.4% of anemia in the country[17]. Fortification of wheat flour with folic acid almost eliminated folate deficiency anemia, to only 0.1% in a cohort of adults >50 years of age.[18].

Fortification impact on prevalence of neural tube defects

Folic acid's ability to prevent NTDs was proven in 1991, 1992, and 1999, when randomized controlled trials showed that multivitamins containing folic acid prevented recurrence[19] and then first occurrence[20]. A large-scale community cohort study in China using only folic acid supplements then showed that folic acid was the nutrient that prevented neural tube defects[Error! Bookmark not defined.]. The inclusion of folic acid in fortification was intended to reach women who, for multiple reasons, may not access folic acid pills prior to pregnancy.

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[12] Colapinto CK, et al. Folate status of the population in the Canadian Health Measures Survey. Canadian Medical Association Journal, 183(2):E100-6, 2011.

[13] Pfeiffer CM, et al. Estimation of Trends in Serum and RBC Folate in the U.S. Population from Pre- to Postfortification Using Assay-Adjusted Data from the NHANES 1988–2010. J Nutr. 2012 May;142(5):886-93. doi: 10.3945/jn.111.156919. Epub 2012 Mar 21.

[14] Tinker SC et al. U.S. women of childbearing age who are at possible increased risk of a neural tube defect-affected pregnancy due to suboptimal red blood cell folate concentrations, National Health and Nutrition Examination Survey 2007 to 2012. Birth Defects Res A Clin Mol Teratol. 2015 Jun;103(6):517-26. doi: 10.1002/bdra.23378. Epub 2015 Apr 17.

[15] Colapinto CK, et al. The direction of the difference between Canadian and American erythrocyte folate concentrations is dependent on the assay method employed: a comparison of the Canadian Health Measures Survey and National Health and Nutrition Examination Survey. Br J Nutr. 2014 December 14; 112(11): 1873–1881.

[16] National Food and Nutrition Centre. Impact of iron fortified flour in child bearing age (CBA) women in Fiji, 2010 report. Suva: National Food and Nutrition Centre; 2012.

[17] Guralnik JM, et al. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood 2004; 104:2263–8.

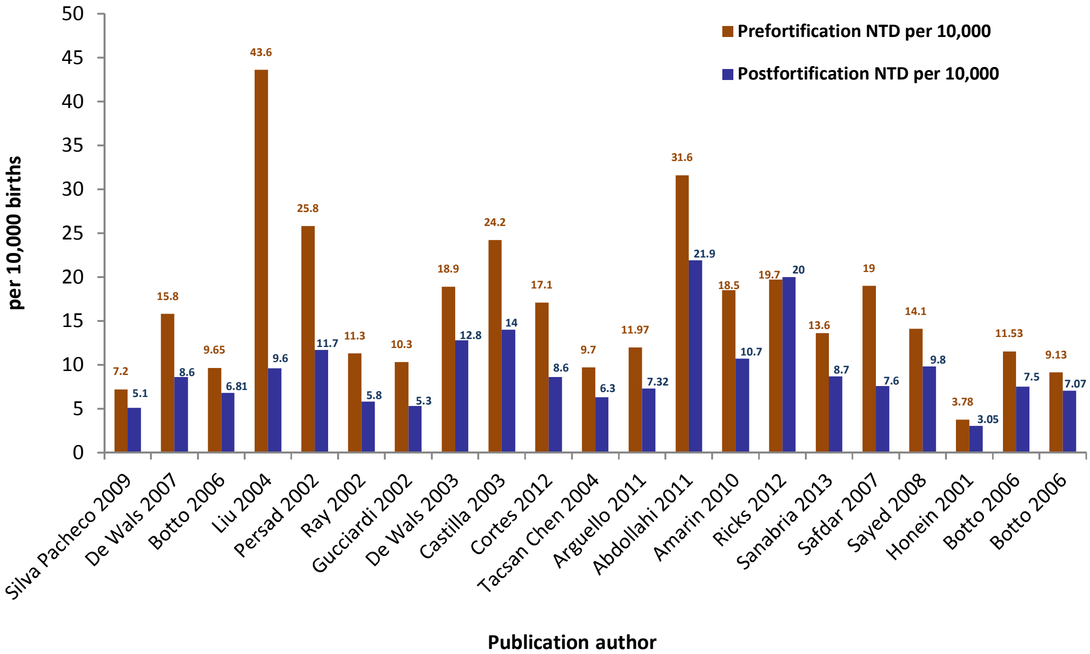
[18] Odewole OA, et al. Near-elimination of folate-deficiency anemia by mandatory folic acid fortification in older US adults: Reasons for Geographic and Racial Differences in Stroke study 2003–2007. American Journal of Clinical Nutrition, 98(4):1042-7, 2013.

[19] MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet. 1991 Jul 20;338(8760):131-7.

[20] Czeizel AE, et al. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992 Dec 24;327(26):1832-5.

Countries that have evaluated the impact of folic acid fortification on the prevalence of neural tube defect rates before and after fortification have similarly found consistent declines in neural tube defects after fortification (Figure 1).

Figure 1: Review of neural tube defect rates in before and after fortification[21]



Folic acid supplementation and adverse outcomes: global data

When reviewing information of adverse outcomes of any intervention, it is essential to focus on high-quality, systematic review or meta-analyses, rather than individual studies. Temporal data such as cross-sectional studies or ecological studies do not indicate cause-effect, especially if other observational studies are inconsistent.

It is also essential to remember that folic acid fortification is always designed to deliver much lower quantities of folic acid compared to supplements. The Recommended Daily Intake of folic acid is 400 micrograms (mcg) daily for adult women of reproductive age. In the United States and Australia, fortification was designed to increase daily intakes by 100-200 mcg[22,23]; in Costa Rica and Chile the mandatory fortification program was designed to deliver 400 mcg of folic acid per day[24,25]. Supplements usually provide 400 mcg or more of folic acid up to 5,000 mcg per pill; older folic acid supplement studies have provided as much as 10,000 mcg of folic acid[26].

[21] Food Fortification Initiative (FFI). Fortifying flour with folic acid to prevent neural tube defects. Atlanta, USA: FFI, 2012 and updated in 2015. www.FFInetwork.org/why_fortify/documents/FortifyToPreventNTDs.pdf. Accessed 25 May 2015.

[22] Yang Q et al. Folic acid source, usual intake, and folate and vitamin B-12 status in US adults: National Health and Nutrition Examination Survey (NHANES) 2003–20061–4. Am J Clin Nutr. 2010 Jan;91(1):64-72.

[23] Dugbaza J, et al. Estimates of Total Dietary Folic Acid Intake in the Australian Population Following Mandatory Folic Acid Fortification of Bread. Journal of Nutrition and Metabolism. Volume 2012.

[24] Hertrampf E, et al. National food-fortification program with folic acid in Chile. Food and Nutrition Bulletin, vol. 29, no. 2 (supplement) 2008.

[25] Tacsan, L. Ministry of Health. Rice Fortification in Costa Rica: a case study. Presentation at Scaling Up Rice Fortification in Asia. Bangkok, Thailand. 2014.

[26] Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington (DC): National Academies Press (US); 1998. Available at https://www.ncbi.nlm.nih.gov/books/NBK114310/pdf/Bookshelf_NBK114310.pdf.

Since folate is utilized in one-carbon metabolism and DNA replication and cell division, concerns over cancer development have been raised[27]. Cancer as a potential adverse outcome of folic acid has been well studied by national scientific committees and taskforces in recent years, utilizing randomized, controlled trials or long-term prospective cohort studies as evidence.

Most of the single studies/reports on the relationship between folic acid and cancer have been based on supplementation-level intakes of folic acid, which are much higher than low levels of folic acid provided by fortification.

All known country reports on systematic reviews on folic acid and cancer and their conclusions are listed below. The list does not include single studies/reports on folic acid and cancer.

- In 2016 Australia updated its review on folic acid cancer, and all-cause mortality and concluded: "No increase in cancer or all-cause mortality can be directly associated with increase in folic acid intakes in adults"[28].
    - The original 2006 review concluded the same[29].
    - Post-fortification, it also found that "very few" adults exceeded the upper limit for folic acid. While 21% of children aged 2-3 years exceeded the upper limit for children, the report concluded, "this is not considered to pose a health risk".
- In 2015 the US National Toxicology Program conducted a review of reviews and found 43 pooled studies and meta-analyses across several cancer outcomes.
    - Forest plots of the extracted review data indicate an overall conclusion of no association between folic acid supplements and cancer outcomes (Appendix, Figure 2)[30].
- In 2012, New Zealand's Ministry of Primary Industries released a scientific evaluation of folic acid fortification and found no relationship between cancer and folic acid: "Folic acid has no significant effect on overall cancer incidence… It is noteworthy that all these trials used supplements with concentrations of folic acid that would have caused higher daily folic acid intakes than would occur with fortified bread."[31]
- In 2008, Ireland's Public Safety Authority summarized the scientific developments on adverse events and found no relationship between cancer and folic acid: "epidemiological data and human studies relating to folic acid and cancer risk are inconsistent and not conclusive"[32]
- In 2008, the Health Council of the Netherlands, an independent scientific advisory body, provided the Minister of Health with a recommendation to include folic acid and the following conclusion on cancer and folic acid: ""However, the findings are not yet strong enough to enable any conclusions to be drawn as to the role of folate in the onset, growth or treatment of cancer"[33].
- In 2006, the United Kingdom's Scientific Advisory Council on Nutrition recommended folic acid fortification and concluded, "the evidence for an association between folic acid and increased or reduced cancer risk in humans is equivocal."[34]

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27 Kim YI (2004). Will mandatory folic acid fortification prevent or promote cancer? Am J Clin Nutr 80(5): 1123-1128.
28 Australian Institute of Health and Welfare. Monitoring the health impacts of mandatory folic acid and iodine fortification. 2016.
29 Food Standards of Australia and New Zealand. Consideration of Mandatory Fortification with Folic Acid. 2006.
30 2015 National Toxicology Program Monograph: Identifying Research Needs for Assessing Safe Use of High intakes of Folic Acid. Available at: https://hawcproject.org/summary/data-pivot/assessment/94/draft-all-pooled-studies/.
31 Government of New Zealand. Scientific evaluation of comments on submissions received on the future of folic acid fortification in New Zealand: MPI Technical Paper No: 2012/25 2012. Available from: https://www.mpi.govt.nz/document-vault/4048.
32 Public Safety Authority. 2008. Report of the Implementation Group on Folic Acid Food Fortification to the Department of Health and Children, Ireland.
33 Health Council of the Netherlands. 2008. Towards an Optimal Use of Folic Acid.
34 Scientific Advisory Council on Nutrition. United Kingdom. 2006. Folate and disease prevention report.

Observational epidemiological studies have suggested relationships between folic acid and various cancers[35,36] but individual studies should be taken into consideration alongside the large volume of meta-analyses of higher-quality randomized controlled trials and cohort studies, which have consistently found no relationship between folic acid and cancer outcomes.

Interactions with vitamin B12 deficiency: masking and cognitive impairment

Megaloblastic anemia can be due to folate deficiency or vitamin B12 deficiency. Because the two vitamins share a metabolic pathway, treating a vitamin B12 deficient patient with folic acid will resolve the megaloblastic anemia but not resolve neurological damage due to vitamin B12 deficiency. This was the basis for the concern over 'masking' vitamin B12 deficiency[37]. However, clinical practice no longer relies on megaloblastic anemia for diagnosing vitamin B12 deficiency, so masking of vitamin B12 deficiency is no longer a concern[31].

Concerns have been raised whether high intake of folic acid could exacerbate cognition decline in older populations, but there are no controlled trials or prospective cohort studies to evaluate for this concern. The available data on folic acid and cognition is cross-sectional or ecological and do not allow for cause-effect conclusions[38,39].

The prevalence of dementia in the United States declined significantly from 2000 to 2012[40]. In the US, folic acid was required to be added to most wheat flour, maize flour, and rice beginning January 1, 1998. In addition, many breakfast cereals are fortified with folic acid, and supplements with folic acid are readily available. The decline in dementia is not associated with folic acid, but it argues against the theory that folic acid contributes to cognitive decline.

Relationship with asthma

Two systematic reviews of the relationship between maternal folic acid supplementation and childhood asthma both concluded that there is no relationship between folic acid supplementation and greater risk for childhood asthma[41,42].

Relationship with autism

Two systematic reviews published in 2016 and 2015 concluded that there is not enough evidence to establish a relationship between maternal exposure to folic acid and autism spectrum disorder.

- Castro et al. "Regarding our main issue, namely the effect of folic acid supplementation, especially in pregnancy, the few and contradictory studies present inconsistent conclusions." [43]
- DeVilbiss et al. "Much of the existing literature on this topic is subject to limitations such as potential confounding by healthy behaviours and other dietary factors, and exposure assessed within limited

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35 Mason JB, et al. (2007) A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles; a hypotheses. Cancer Epidemiology Biomarkers Prev.; 16; 1325 – 1329.
36 Hirsch S, et al. (2008) Colon Cancer in Chile before and after the start of the flour fortification program with folic acid. European Journal of Gastroenterology & Hepatology.
37 Crider KS, Bailey LB, Berry RJ. Folic acid food fortification-its history, effect, concerns, and future directions. Nutrients. 2011;3(3):370-84.
38 Carmel R. Does high folic acid intake affect unrecognized cobalamin deficiency, and how will we know it if we see it? Am J Clin Nutr. 2009;90(6):1449-50.
39 Berry RJ, et al. Cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr. 2007;86(1):265-7; author reply 7-9.
40 Langa KM, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. JAMA Internal Medicine. 2016. doi:10.1001/jamainternmed.2016.6807.
41 Crider KS, et al. Prenatal folic acid and risk of asthma in children: a systematic review and meta-analysis. Am J Clin Nutr. 2013 Nov;98(5):1272-81. doi: 10.3945/ajcn.113.065623. Epub 2013 Sep 4. Review.
42 Brown SB, et al. Maternal folate exposure in pregnancy and childhood asthma and allergy: a systematic review. Nutr Rev. 2014 Jan;72(1):55-64. Review.
43 Castro K et al. Folic acid and autism: What do we know? Nutritional Neuroscience Vol. 19 , Iss. 7,2016

exposure windows. As the existing evidence is inconclusive, further research remains to be conducted in order to verify this hypothesis."[44]

Unmetabolized folic acid

Unmetabolized folic acid is any amount of folic acid that is found in the blood because it has not been converted into other forms of folate or removed from the body through urination. Folic acid is absorbed by the intestines into the bloodstream, and then converted to other forms of folate by the liver. The liver is capable of processing only a certain amount of folic acid at one time. Unused folic acid in the blood goes to the kidneys and leaves the body in urine[45].

People taking a single dose of folic acid of more than 200 mcg can have some unmetabolized folic acid circulating in their blood[46,47]. As noted, people in the United States have multiple ways to access folic acid, therefore US residents may have varying amounts of unmetabolized folic acid in their blood [44,48-50]. Since the beginning of mandatory folic acid fortification, most people have had some unmetabolized folic acid circulating in their blood[48]. Yet no confirmed health risks have been found from unmetabolized folic acid[51-53]. A recent review found no evidence of harmful effects of unmetabolized folic acid in the blood of infants[54].

Folic acid supplementation and emerging beneficial outcomes: global data

Folic acid conclusively prevents neural tube defect births. There is also emerging evidence from high quality studies that indicate that folic acid supplementation is also beneficial for other health conditions.

Prevention of primary stroke in adults with hypertension

Recently a randomized controlled trial among adults with hypertension in China found that those who took 800 mcg/d of folic acid had a 21% reduction in the occurrence of first stroke[55].

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[44] DeVilbiss EA, et al. Maternal folate status as a risk factor for autism spectrum disorders: a review of existing evidence. British Journal of Nutrition, Volume 114, Issue 5 September 2015, pp. 663-672.

[45] Bailey LB, Stover PJ, McNulty H, Fenech MF, Gregory JF, 3rd, Mills JL, Pfeiffer CM, Fazili Z, Zhang M, Ueland PM, et al. Biomarkers of Nutrition for Development-Folate Review. J Nutr 2015;145(7):1636S-80S. doi: 10.3945/jn.114.206599.

[46] Kelly P, McPartlin J, Goggins M, Weir DG, Scott JM. Unmetabolized folic acid in serum: acute studies in subjects consuming fortified food and supplements. Am J Clin Nutr 1997;65(6):1790-5.

[47] Sweeney MR, McPartlin J, Weir DG, Daly L, Scott JM. Postprandial serum folic acid response to multiple doses of folic acid in fortified bread. Br J Nutr 2006;95(1):145-51. doi: S0007114506000183 [pii].

[48] Sweeney M, McPartlin J, Scott J. Folic acid fortification and public health: Report on threshold doses above which unmetabolised folic acid appear in serum. BMC Public Health 2007;7(1):41.

[49] Kalmbach RD, Choumenkovitch SF, Troen AM, D'Agostino R, Jacques PF, Selhub J. Circulating folic acid in plasma: relation to folic acid fortification. Am J Clin Nutr 2008;88(3):763-8. doi: 88/3/763 [pii].

[50] Pfeiffer CM, Sternberg MR, Fazili Z, Yetley EA, Lacher DA, Bailey RL, Johnson CL. Unmetabolized Folic Acid Is Detected in Nearly All Serum Samples from US Children, Adolescents, and Adults. The Journal of nutrition 2015;145(3):520-31. doi: 10.3945/jn.114.201210.

[51] Morris MS, Jacques PF, Rosenberg IH, Selhub J. Circulating unmetabolized folic acid and 5-methyltetrahydrofolate in relation to anemia, macrocytosis, and cognitive test performance in American seniors. The American journal of clinical nutrition 2010;91(6):1733-44. doi: 10.3945/ajcn.2009.28671.

[52] Troen AM, Mitchell B, Sorensen B, Wener MH, Johnston A, Wood B, Selhub J, McTiernan A, Yasui Y, Oral E, et al. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. The Journal of nutrition 2006;136(1):189-94.

[53] Sweeney MR, Staines A, Daly L, Traynor A, Daly S, Bailey SW, Alverson PB, Ayling JE, Scott JM. Persistent circulating unmetabolised folic acid in a setting of liberal voluntary folic acid fortification. Implications for further mandatory fortification? BMC Public Health 2009;9:295. doi: 1471-2458-9-295 [pii]10.1186/1471-2458-9-295.

[54] Obeid R, Herrmann W. The emerging role of unmetabolized folic acid in human diseases: myth or reality? Curr Drug Metab 2012;13(8):1184-95.

[55] Huo, Y., et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. JAMA, 2015. 313(13): p. 1325-35.

Appendixes

Table 5: Countries with Mandatory wheat flour fortification standards, by nutrients included in standards[56]

Country Name	Iron	Folic acid	Thiamin	Riboflavin	Niacin	Zinc	B12	B6	Vitamin A	Calcium	Vitamin D
Congo	Yes	No	No	No	No	No	No	No	No	No	No
Philippines	Yes	No	No	No	No	No	No	No	Yes	No	No
United Kingdom	Yes	No	Yes	No	Yes	No	No	No	No	Yes	No
Venezuela	Yes	No	Yes	Yes	Yes	No	No	No	No	No	No
Viet Nam	Yes	No	No	No	No	Yes	No	No	No	No	No
Antigua and Barbuda	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Argentina	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Australia	No	Yes	Yes	No	No	No	No	No	No	No	No
Bahamas	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Bahrain	Yes	Yes	No	No	No	No	No	No	No	No	No
Barbados	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Belize	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No
Benin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Bolivia	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Brazil	Yes	Yes	No	No	No	No	No	No	No	No	No
Burkina Faso	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Burundi	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Cameroon	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Canada	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Cape Verde	Yes	Yes	No	No	No	No	No	No	No	No	No
Chile	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Colombia	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Costa Rica	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Cote d'Ivoire	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Cuba	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Djibouti	Yes	Yes	No	No	No	Yes	No	No	No	No	No
Dominica	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Dominican Republic	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Ecuador	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Egypt	Yes	Yes	No	No	No	No	No	No	No	No	No
El Salvador	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Fiji	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Ghana	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Grenada	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Guatemala	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Guinea	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Guyana	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Haiti	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Honduras	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Indonesia	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	No
Iran	Yes	Yes	No	No	No	No	No	No	No	No	No
Iraq	Yes	Yes	No	No	No	No	No	No	No	No	No
Jamaica	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No

[56] Food Fortification Initiative Database, 2016. Individual country profiles with fortification standards available at: http://ffinetwork.org/country_profiles/index.php. Aggregated database available upon request: info@ffinetwork.org.

Jordan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Kazakhstan	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Kenya	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Kosovo	Yes	Yes	No	No	No	No	No	No	No	No	No
Kuwait	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No
Kyrgyzstan	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Liberia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Malawi	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Mali	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Mauritania	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Mexico	Yes	Yes	No	No	No	No	No	No	No	No	No
Moldova	Yes	Yes	No	No	No	No	No	No	No	No	No
Morocco	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Mozambique	Yes	Yes	No	No	No	Yes	Yes	No	No	No	No
Nepal	Yes	Yes	No	No	No	No	No	No	Yes	No	No
Nicaragua	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Niger	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Nigeria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Oman	Yes	Yes	No	No	No	No	No	No	No	Yes	No
Palestine Occupied Territory	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Panama	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Paraguay	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Peru	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Saint Kitts and Nevis	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes
Saint Lucia	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Saint Vincent and the Grenadines	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No
Saudi Arabia	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Senegal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Sierra Leone	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Solomon Islands	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
South Africa	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Suriname	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Tanzania	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Togo	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Trinidad and Tobago	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes
Turkmenistan	Yes	Yes	No	No	No	No	No	No	No	No	No
Uganda	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
United States of America	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Uruguay	Yes	Yes	No	No	No	No	Yes	No	No	No	No
Uzbekistan	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Yemen	Yes	Yes	No	No	No	No	No	No	No	No	No
Zimbabwe	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Total	84	80	66	64	63	31	24	21	13	4	4

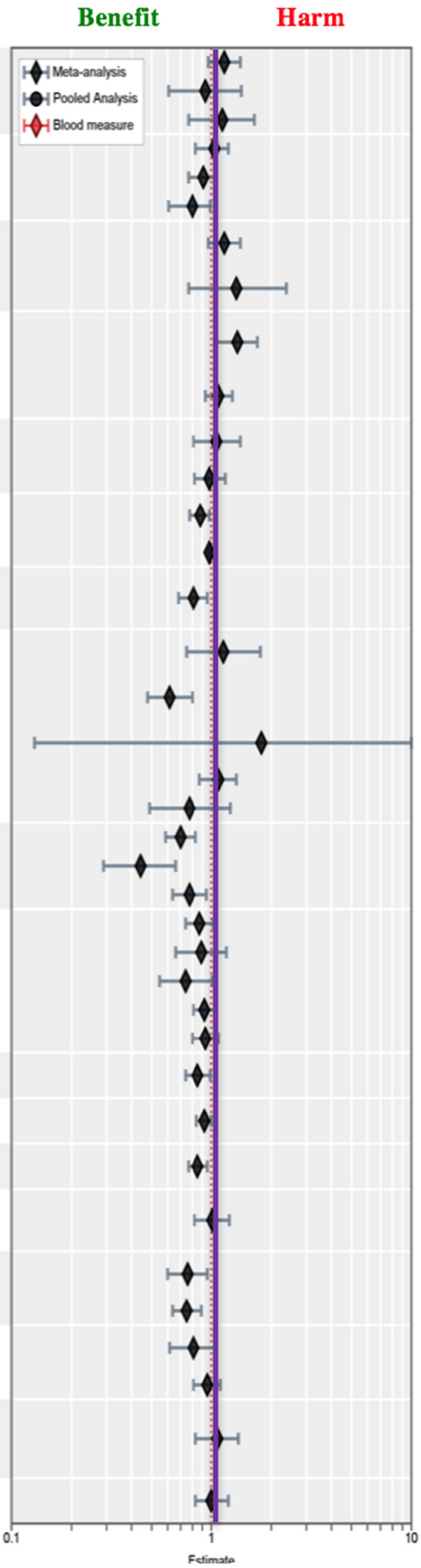
Table 6: Countries with mandatory rice fortification, by nutrients included in standards[56]

Country Name	Iron	Thiamin	Niacin	Folic acid	B12	Zinc	B6	Vitamin E	Selenium
Costa Rica	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Philippines	Yes	No	No	No	No	No	No	No	No
Papua New Guinea	Yes	Yes	Yes	No	No	No	No	No	No
Nicaragua	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Panama	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
United States of America	Yes	Yes	Yes	Yes	No	No	No	No	No
Total	**5**	**5**	**5**	**4**	**3**	**3**	**2**	**1**	**1**

Figure 2: Folic Acid - Cancer Pooled and Meta-analyses (2015)[57]

Click on the study name and result from this website to access additional information on the studies listed.

Study	Protocol	Exposure	Result Label	N (subjects)
Carroll, 2010	Folic acid and prevention of colorectal cancer	folic acid supplementation	Adenoma recurrence, Folic acid vs. placebo (2 studies)	749
			Adenoma recurrence, Folic acid vs. placebo (3 studies)	840
			Colorectal cancer incidence, plus antioxidants	11,062
Chuang, 2013	Circulating folate and colorectal cancer	Circulating folate	Colorectal cancer, circulating folate, Microbiological assay	5,831
			Colorectal cancer, circulating folate, Overall	10,516
			Colorectal cancer, circulating folate, Radioimmunoassay	4,685
Cooper, 2010	Folic acid and colorectal adenomas	Folic acid	Recurrence of any adenoma, Folic acid alone vs. placebo alone	749
			Incidence of advanced adenoma, Folic acid alone vs. placebo alone	749
Fife, 2011	RCTs for Folic Acid Supplementation and Colorectal Cancer Risk	folic acid supplementation	adenoma and advanced adenoma, folate supplementation, longer follow-up, >3 years	6,736
			adenoma and advanced adenoma, folate supplementation, shorter follow up, <4 years	3,686
Figueiredo, 2011	AFPPS, NHS/HPFS, and ukCAP, 1994-2001	Folic acid	Advanced adenoma within 42 months, Folic acid	1,922
			Any adenoma within 42 months, Folic acid	1,957
Heine-Bröring, 2015	Dietary supplement use and colorectal cancer risk	folic acid	colorectal cancer, folic acid, highest-lowest supplement use	291,006
			colorectal cancer, intake of supplemental folic acid	291,006
Hutter, 2012	Colorectal cancer and gene-environment inteactions	Dietary folate	Colorectal cancer, Folate	16,843
Ibrahim, 2010	Folic acid and colorectal adenoma recurrence	Folic acid supplementation	Colorectal adenomas, 0.5mg/day folic acid supplementation, random effects	419
			Colorectal adenomas, 1mg/day folic acid supplementation, random effects	1,041
			Colorectal adenomas, 5mg/day folic acid supplementation, random effects	20
			Colorectal adenomas, folic acid supplementation, fixed effects	1,486
			Colorectal adenomas, folic acid supplementation, random effects	1,480
Kantor, 2014	GECCO and CCFR studies	dietary folate	colorectal cancer, dietary folate	18,440
			colorectal cancer, dietary folate, case–control studies	10,798
			colorectal cancer, dietary folate, nested case–control studies	7,642
Kennedy, 2011	Folate intake and the risk of colorectal cancer	dietary folate	colorectal cancer, dietary folate, case control	3,276
			colorectal cancer, dietary folate, case control, men only	695
			colorectal cancer, dietary folate, case control, women only	691
			colorectal cancer, dietary folate, cohort	472,531
			colorectal cancer, dietary folate, cohort, women only	291,720
Kennedy, 2011	Folate intake and the risk of colorectal cancer	total folate	colorectal cancer, total folate, case control	1,679
Kim, 2010	Pooled analyses of folate intake and colon cancer	dietary folate intake	colon cancer, folate intake, dietary	725,134
Kim, 2010	Pooled analyses of folate intake and colon cancer	total folate intake	colon cancer, folate intake, total	526,166
Qin, 2013	Folic acid supplementation and cancer risk	folic acid treatment	colorectal cancer, folic acid	33,824
Sanjoaquin, 2005	Folate intake and colorectal cancer	dietary folate intake	colorectal cancer, dietary folate, case-control	15,842
			colorectal cancer, dietary folate, cohort	2,394
Sanjoaquin, 2005	Folate intake and colorectal cancer	total folate intake	colorectal cancer, total folate, case-control	2,467
			colorectal cancer, total folate, cohort	2,689
Vollset, 2013	Folic acid supplementation and site-specific cancer incidence	folic acid	cancer incidence; colorectal; folic acid	49,621
Wien, 2012	Cancer risk with folic acid supplements	folic acid intervention	colon and rectum cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control	32,639



[57] Health Assessment Workspace Collaborative. https://hawcproject.org/summary/data-pivot/assessment/94/draft-all-pooled-studies/