Harmonization Workshop for Wheat & Maize Flour Fortification

Folic Acid and Vitamin B12 Work Groups
Nairobi, Kenya
April 19, 2010

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CDC

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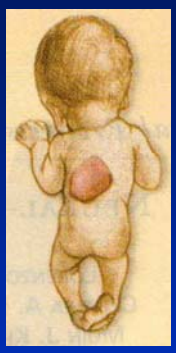
Main topics

- Impact of folic acid and B12 fortification worldwide
  - The scope of the problem of neural tube defects
  - The burden of folic acid deficiency/insufficiency
  - The positive effects of folic acid fortification on NTDs
- Folic acid safety/potential adverse outcomes
  - History of masking
  - Tolerable upper level (1,000 mcg)
  - Sources of folic acid from foods
  - Potential adverse outcomes
- FFI workgroups on folic acid and vitamin B12
- WHO Consensus Statement on Fortification

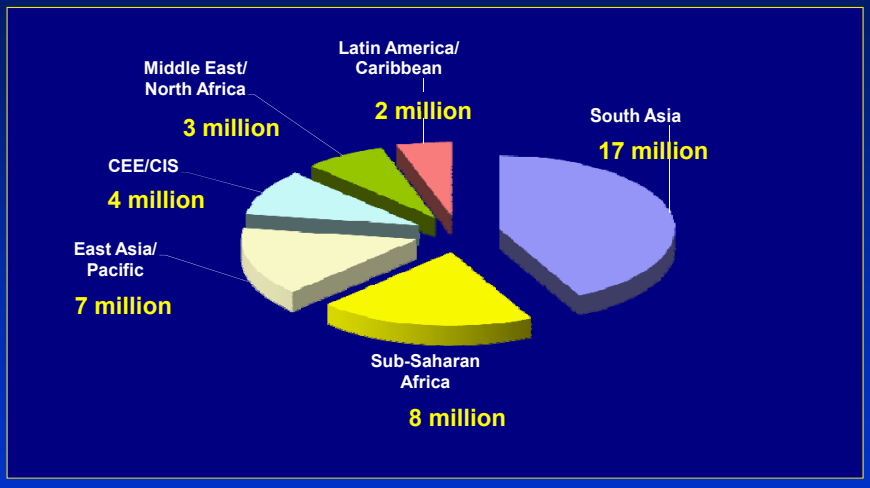
Neural tube defects

- **Serious birth defects**
  - spina bifida and anencephaly
- **> 1 of 1,000 pregnancies**
- **> 300,000 yearly worldwide**



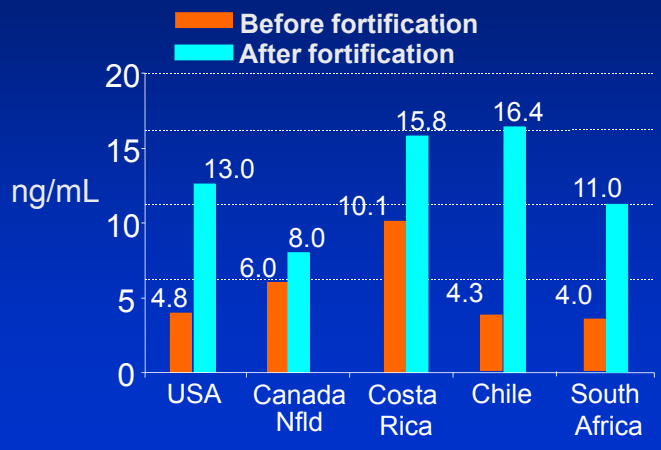
- **Comprehensive, robust data**
  - Randomized controlled trials
  - Consistent case-control studies
  - Occurrence and recurrence
  - Both multivitamins and folic acid alone
- **Increased consumption of folic acid can prevent 50-80% NTDs**
- **Fortification targets NTD prevention, not classical deficiency**

Global Burden of Folic Acid Deficiency

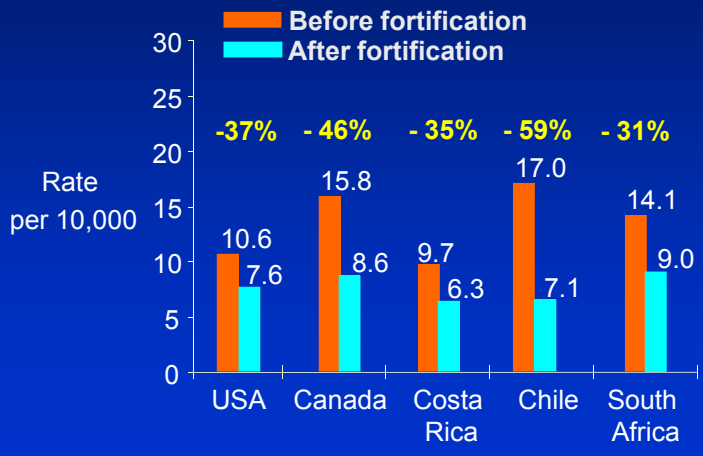


41 M newborns still unprotected each year

Selected serum folate changes (ng/mL) before and after folic acid fortification



Selected worldwide NTD prevalence changes before and after folic acid fortification



United States
Economic Evaluation of Folic Acid Fortification

In 1998 U.S. fortified wheat flour at 140 mcg/ 100g flour

- Reduction in NTDs -- 43%

- Cost of fortification- $3 million per year ($ 1)
- Direct cost averted- $145 million per year ($45)

Grosse, Waitzman, Romano, Mulinare (*Am J Public Health*, 2005)

South Africa
Economic Evaluation of Folic Acid Fortification

In 2004, S. Africa fortified flour with folic acid:

- **Wheat flour at 150 mcg /100g**
- **Maize meal at 220 mcg /100g**

- **Reduction of NTDs -- 31%**
- **Cost of fortification -- R$1.4 million/yr (R$1)**
- **Est. direct costs averted -- R$40 million/yr (R$30)**

(Sayed, Bourne, Nixon, and Henderson, *BDRA* 2008)

Evaluation and monitoring of the impact of flour fortification with folic acid to prevent spina bifida and anencephaly

Blood folates ↑

SBA prevalence rates ↓

Cost benefit analyses + + +

Folic acid safety

History of masking and the UL

Other considered adverse outcomes

History of "masking" B12 deficiency and pernicious anemia (1940's)

- 1926 – Minot and Murphy reported 45 patients with pernicious anemia (PA) cured by eating raw liver.
- 1930s – Liver extracts developed to treat PA
  - Taken orally or by injection
- 1943 – Pure crystalline form of folic acid (FA)
- 1945 – FA shown to treat megaloblastic anemia
- 1947 – First case reports of "masking"
- 1948 – Pure vitamin B_{12} produced

Historical Reviews. *British J Haemat,* 2000, 2001

State of medical knowledge about megaloblastic anemia in 1940s

- Diagnosis
  - Blood smear was the only diagnostic test
  - No idea that there would be more than one cause
  - No bioassays for vitamin B_{12} or folate
- Treatment
  - Raw liver and liver extract effective
  - Folic acid became available before vitamin B_{12} was available
  - Folic acid was seen as a "wonder" treatment

Impact of changes in therapy of megaloblastic anemia in 1940s

- Patients with pernicious anemia switched from liver extract therapy to high dosage folic acid - usually 5,000 to 20,000 mcg/day
- Varied clinical response to many years of treatment with high dose folic acid
  1. No anemia - Probably did not have pernicious anemia
  2. Developed anemia within months - Switched back to liver extract therapy
  3. Developed anemia slowly - ("masking") - usually after more than 2 years and irreversible vitamin B-12 neuropathy progressed

Summary of evidence for "masking"

- 255 case reports contained in 23 articles
  - Most had pernicious anemia before FA use
  - 155 cases had neurological manifestations - the same neurological manifestations seen in pernicious anemia
  - Case studies could not distinguish between preexisting damage from pernicious anemia and damage attributed to use of 5,000 μg folic acid per day
  - Almost no reports since 1960

Institute of Medicine 1998

Tolerable Upper Level

IOM Definition of Tolerable Upper Intake Level

- "Maximum daily intake levels at which no risk of adverse health effects is expected for almost all individuals in the general population-including sensitive individuals-when the nutrient is consumed over long periods of time."

Institute of Medicine 2000

Tolerable Upper Intake Level (UL)

- Lowest Observed Adverse Effects Level (LOAEL) of 5,000 μg of folic acid daily is used as usual intake, above which risk begins.
- 5-fold uncertainty factor divided into LOAEL to derive UL for folic acid. - 1,000 μg/day
- UL intended to be usual intake level at which no one would exceed the LOAEL of 5,000 μg/day.

Institute of Medicine 1998, 2000

Summary of meaning of UL

- UL is not a limit
- UL is not a level where potential risk begins.
- Only synthetic folic acid important.
- UL for folic acid is not based on direct toxicity, but is an attempt to prevent a vitamin B12 problem.

Sources of folic acid

Comparing the Strategies

INTERVENTIONS	ADVANTAGES	CHALLENGES
✘ Supple-mentation	✓ Immediate effects	✓ Higher costs ✓ Requires compliance/change in behavior ✓ Covers only certain groups of population
✘ Fortification	✓ Highly cost-effective ✓ Sustainable ✓ Wide coverage	✓ Requires participation of many groups - food industry, government, scientists, etc
✘ Dietary Diversification	✓ Natural ✓ Other added health benefits	✓Higher costs ✓ Requires change in eating behavior ✓ Requires economic development ✓ Requires changes in agriculture policy

How much folic acid needed to cause an adverse outcome?

What are the sources of folic acid?

Folic Acid

- Is folic acid from supplements and breakfast cereals?
- Is folic acid from fortified foods?

Sources and amounts of folic acid, U.S. – NHANES, 2003-2006

Folic Acid-Containing Supplements (SUP)

~400 µg / supplement (voluntary)

Folic Acid Fortified "Ready-to Eat" Breakfast Cereals (RTE)

Up to 400 µg / serving (voluntary)

Folic Acid Enriched Cereal Grain Products (ECGP)

100-150 µg / day (mandatory)

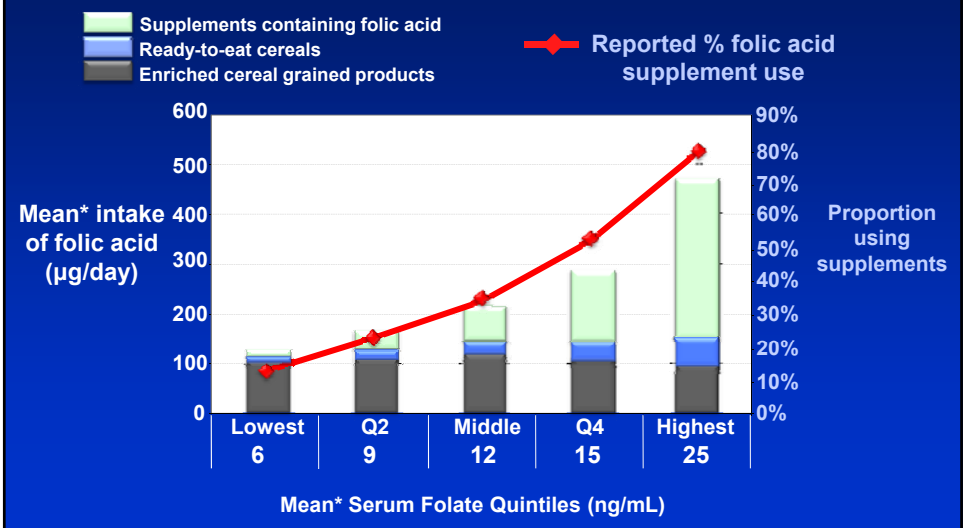
Are You Hungry?
Daily Intake Equivalent of 400 µg of Folic Acid

- 4 slices of fried beef liver
- 44½ medium ripe tomatoes
- 14½ cups of raw broccoli
- 17½ cups of orange juice
- 19½ cups of raw green beans
- 5½ cups of black beans
- 200 medium red apples

Sources of folic acid worldwide

- **Folic acid**
  1. **Supplements containing folic acid**
     - Important source in United States
     - Limited use in other areas of the world
  2. **Ready-to-eat breakfast cereals (RTE)**
     - Limited use in many areas of the world
  3. **Mandatory fortification**
     - Principal source for developing new fortification policies for populations globally

Mean Folic Acid Intake, Enriched Cereal-Grain Products, RTE Cereals & Supplements by Serum Folate Quintiles NHANES 2001-2004, ≥19 years, n=8,655



* Geometric means

25

Adapted from Yeung, LY et al. *JAMA* 2008;300:2486-7

Definition: 4 folic acid consumption groups

- ***ECGP only:***
  - ***ECGP = Enriched cereal grain products with folic acid***

- ***ECGP + RTE:***
  - ***RTE = ready-to-eat cereals with folic acid***

- ***ECGP + SUP:***
  - ***SUP = supplements***

- ***ECGP + RTE + SUP***

Usual total daily folic acid intake by folic acid consumption group,

U.S. non-pregnant adults ≥ 19 years

Folic acid consumption group:	% of US adults	*Usual total daily folic acid intake*	
		Median, µg/d (25th – 75th percentile)	% (95% CI) consuming >1000 µg/d
All ≥ 19 years	100%	288 (160 - 462)	2.7 (1.9-3.5)
ECGP only	42%	138 (106 – 176)	0
ECGP+RTE	18%	274 (230 – 324)	0
ECGP+SUP	25%	479 (360 – 610)	5.5 (3.0-8.0)
ECGP+RTE+SUP	15%	635 (512 – 797)	9.4 (5.5-13.3)

Usual intake of folic acid,
N=8,258
NHANES, 2003 – 2006

Yang QH et.al. AJCN, published online

Summary

Median intakes, blood folate concentrations and % exceeding UL by sources of folic acid

Folic acid consumption group:	Median usual intake µg/d	Blood concentrations		Percentage with usual intake >1000 µg/d
		serum folate ng/mL	RBC folate ng/mL	
ECGP only	138µg	9.4	234	0%
ECGP+RTE	274µg	12.1	273	0%
ECGP+RTE+SUP	635µg	16.9	329	9%
ECGP ± RTE + >400 µg/d SUP	983µg	19.0	356	48%

Yang QH et.al. AJCN 2010;91:64-72

Usual intake of folic acid,
U.S. non-pregnant adults, ≥ 19 years
NHANES, 2003 – 2006

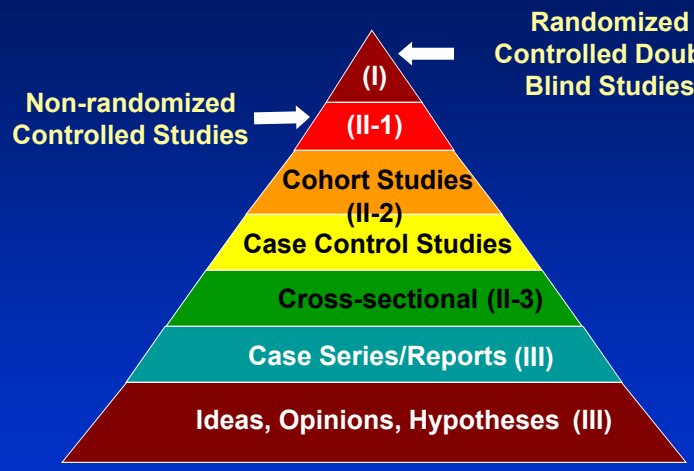
Potential adverse outcomes associated with higher folic acid intake

- Mask diagnosis of the anemia of vitamin B12 deficiency
- "High FA, low B12 status"
  - Possibility of neurological damage of B12 deficiency (≥5,000 µg/d)
  - Insulin resistance (500 µg/d)
- Twinning, miscarriage (supplements)
- Effects on drug therapy of FA sensitive patients (epilepsy, chemotherapy)
- Cognitive impairment in seniors (high folate status)
- Unmetabolized folic acid (bolus > 200 µg/d)
- DNA methylation
- Respiratory distress/asthma
- Colorectal cancer incidence, recurrence (1,000µg/d)

Interpreting folic acid studies

- Randomized studies - use of folic acid
  - Multivitamin – users vs. non-users
- Source of blood folate
  - Folic acid in fortified food
  - Supplements containing folic acid
- Folic acid intake required to achieve higher blood folate concentrations.
- Study design limitations

Ranking the Quality of Evidence*



* Modified slightly from USPSTF Guide to Clinical Preventive Services

High folate and low vitamin B12 status

High folate and low vitamin B12 status

Vitamin B_{12} and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study

C. S. Yajnik · S. S. Deshpande · A. A. Jackson · H. Refsum · S. Rao · D. J. Fisher · D. S. Bhat · S. S. Naik · K. J. Coyaji · C. V. Joglekar · N. Joshi · H. G. Lubree · V. U. Deshpande · S. S. Rege · C. H. D. Fall

Yajnik, et.al. Diabetologia (2008) 51:29-38

Methods

- Longitudinal study in rural India
- Pregnant women (n=700) from 6 villages in India
- Children (n=674) at 6 years of age
- Measure of insulin resistance: Homeostatic model assessment of insulin resistance (HOMA-R)
- Use of folic acid not randomized

Yajnik, et.al. Diabetologia (2008) 51:29-38

Results

"Low maternal vitamin B12 and high folate status may contribute to the epidemic of adiposity and type 2 diabetes in India"

Yajnik, et.al. Diabetologia (2008) 51:29-38

High folate and low vitamin B12 status

Antenatal Micronutrient Supplementation Reduces Metabolic Syndrome in 6- to 8-Year-Old Children in Rural Nepal[1,2]

Christine P. Stewart,[3]* Parul Christian,[3] Kerry J. Schulze,[3] Steven C. LeClerq,[3,4] Keith P. West Jr,[3] and Subarna K. Khatry[4]

Stewart CP, et.al J Nutr 139: 1575–1581, 2009.

Community-based randomized control trial with 5 arms of antenatal micronutrients in rural Nepal, 1999-2001

- Control Vitamin A (1 mg RE)
- Vitamin A + FA (400µg)
- Vitamin A + FA + iron (60 mg)
- Vitamin A + FA + iron + zinc (30 mg)
- Vitamin A + FA + iron + zinc + 11 additional vitamins and minerals

Stewart CP, et.al J Nutr 139: 1575–1581, 2009.

Follow-up assessments - 2006

- Children 6 to 8 years
- 3,900 children surviving to 6 months
- 3,524 enrolled (~ 93%:93 to 95% by group)
- Measurements: BP's, anthropometry, waist, skin-folds, triglycerides, cholesterol, glucose, HBA1c, insulin, creatinine, microalbuminuria
- 67% - fasting (insulin)

Stewart CP, et.al J Nutr 139: 1575–1581, 2009.

Results

"None of the micronutrient supplement combinations affected blood pressure, cholesterol, triglycerides, glucose, insulin, or HOMA. … a reduced risk of metabolic syndrome in the folic acid group"

Stewart CP, et.al J Nutr 139: 1575–1581, 2009.

The India study data are observational and should not be used to make causal inferences.

The Nepal data are from a follow-up study of an RCT, in which antenatal use of folic acid was randomized.

Potential adverse outcomes of folic acid from mandatory fortification

Is flour fortification with folic acid related to causing cancer?

- **Colorectal cancer incidence**
  - **Mason 2007 – United States and Canada**
  - **Hirsch 2009 – Chile**

Proposed effect of folic acid
Hypothesized Risk: Increase Colorectal Cancer

Hypothesis

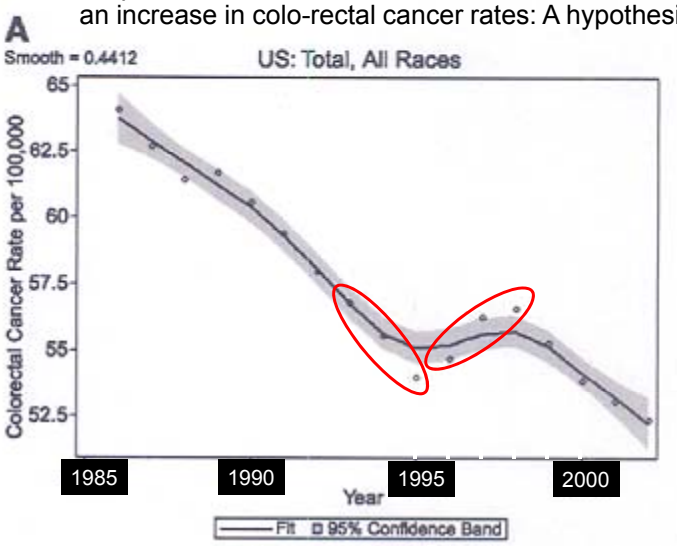
A Temporal Association between Folic Acid Fortification and an Increase in Colorectal Cancer Rates May Be Illuminating Important Biological Principles: A Hypothesis

Joel B. Mason,[1,2] Aaron Dickstein,[2] Paul F. Jacques,[1] Paul Haggarty,[3] Jacob Selhub,[1] Gerard Dallal,[1] and Irwin H. Rosenberg[1,2]

[1]Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University; [2]Tufts University School of Medicine, Boston, Massachusetts; and [3]Rowett Research Institute, University of Aberdeen, Aberdeen, United Kingdom

Mason et al. *Cancer Epidemiol. Biomarkers Prev.* 2007;16(7):1325-1329.

A temporal association between folic acid fortification and an increase in colo-rectal cancer rates: A hypothesis.



Fortification of foods with folic acid
Kaiser Permanente, S. CA, 1994-1999

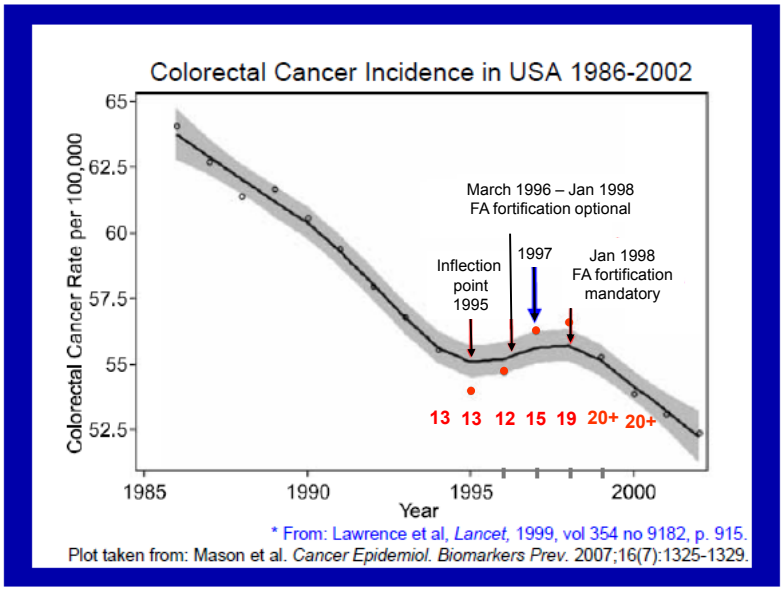
Lawrence JM et al. (Letter) NE JM 2000;343:970-72

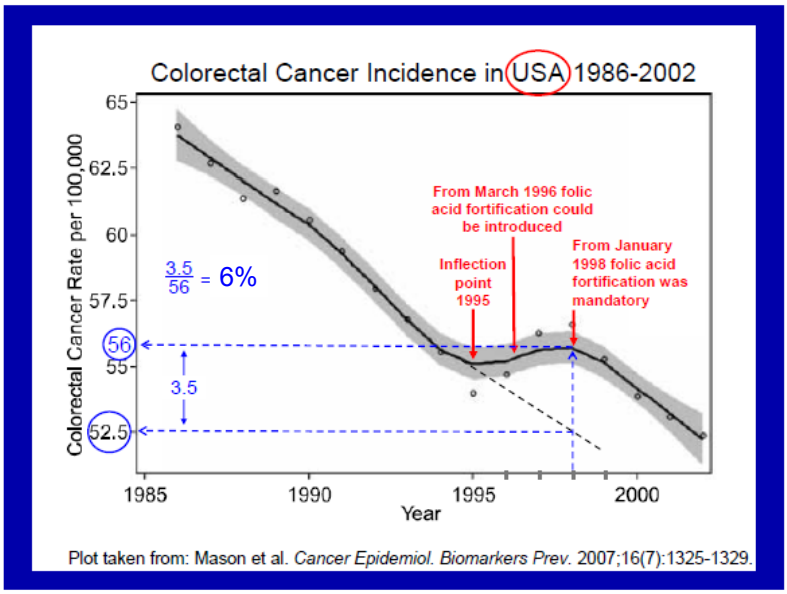
TABLE 1. SERUM FOLATE LEVELS, 1994 THROUGH 1999.*

YEAR	NO. OF TESTS	RATE OF TESTING	SERUM FOLATE <2.7 ng/ml	SERUM FOLATE ≥20 ng/ml	MEDIAN SERUM FOLATE VALUE
		per 1000 members	no. of tests (%)		ng/ml
1994	14,493	7.3	183 (1.3)	3,709 (25.6)	12.6
1995	14,749	6.7	186 (1.3)	3,652 (24.8)	12.7
1996	17,642	7.5	223 (1.3)	4,130 (23.4)	11.7
1997	22,805	8.9	134 (0.6)	7,815 (34.3)	14.9
1998	28,662	10.2	89 (0.3)	12,990 (45.3)	18.7
1999	31,309	10.8	52 (0.2)	16,527 (52.8)	20 +

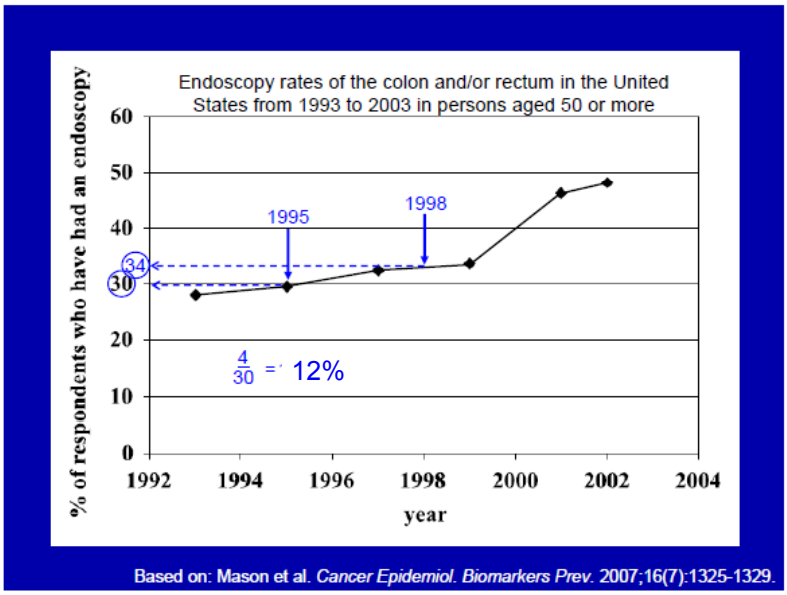
*Data for 1994 through 1998 are from Lawrence et al.[3]

Folates measured using Advia Centaur immunoassay system, Bayer Diagnostics





Analysis by Sir Nicholas Wald, Jan 2009



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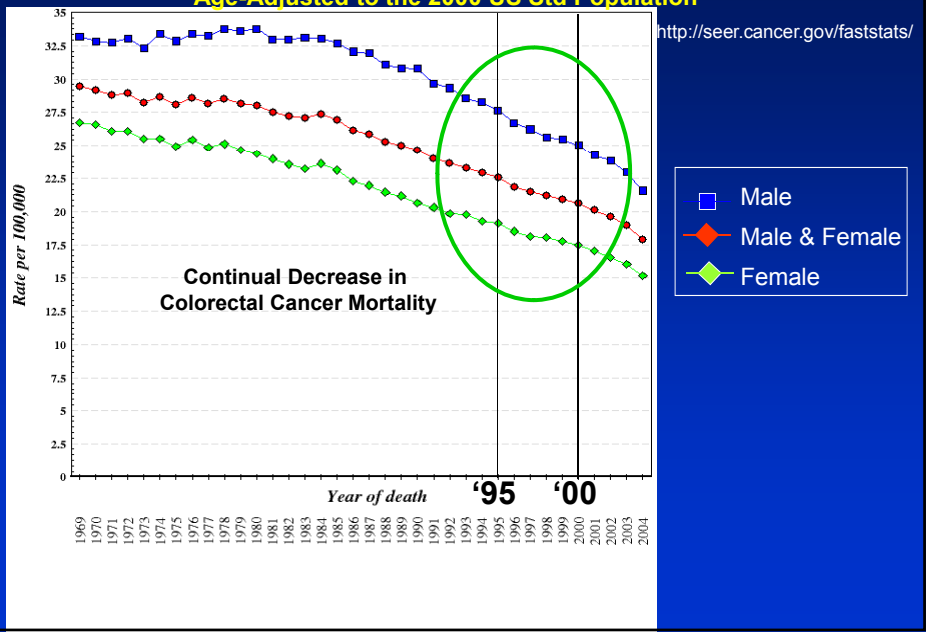
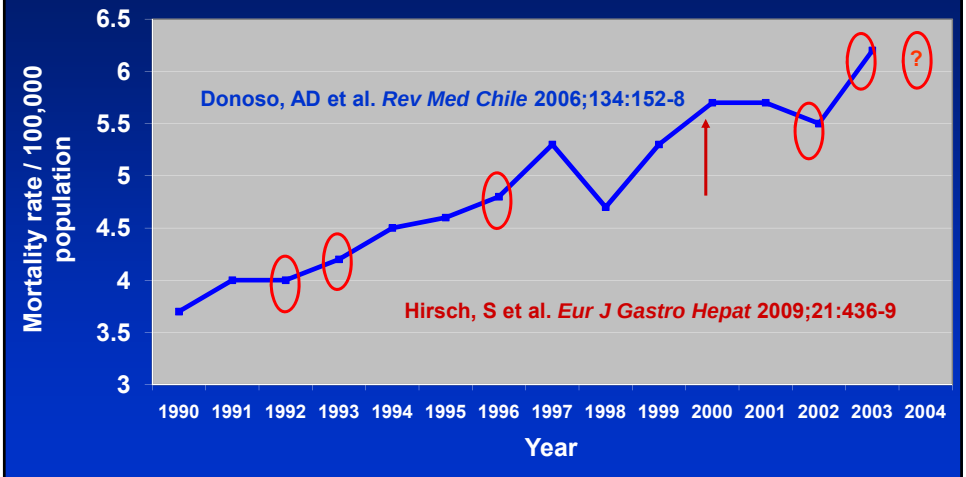


Mason et al. Summary

- Hypothesis that proposes an increase in colon cancer cases in United States in mid to late 1990s from folic acid fortification:
  - Timing of diagnosis and measured blood folates are not quite in sync
  - 6% increase in diagnosis of colon cancer could be associated to the 12% increase in endoscopy usage
  - Observed deaths from colon cancer not necessarily consistent with the hypothesis

Crude CRC mortality rate Chile 1990-2003



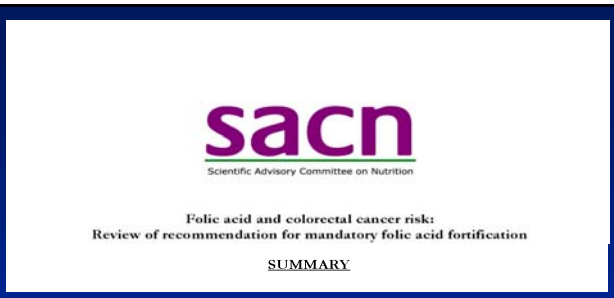
Donoso, AD et al. *Rev Med Chile* 2006;134:152-8

Evaluation of benefits and risks of folic acid fortification by other countries

- FSANZ – Food Standards Australia and New Zealand
- FSA – Food Safety Agency – Ireland
- HCN – Health Council of the Netherlands
- FSA – Food Standards Agency – UK
  - SACN – Scientific Advisory Committee on Nutrition
  - CoC – Committee on Carcinogenicity

Scientific Advisory Committee on Nutrition (SACN)

- In 2006 SACN recommended mandatory fortification of flour with folic acid to the UK Food Standards Agency.
- In June 2007, Mason and Cole papers published.
- In October 2007, the Chief Medical Officer requested advice from SACN on potential adverse effects of folic acid on colorectal cancer risk.
- A working group comprising members of SACN and experts in cancer and cancer epidemiology, was set up to evaluate the evidence.



The Scientific Advisory Committee on Nutrition (SACN):

In 2007 SACN was asked by the UK Food Safety Authority to review potential adverse effects of folic acid on colorectal cancer risk. Members of SACN and experts in cancer epidemiology reviewed the evidence.

In April 2009 SACN concluded that there were currently insufficient data on the Relation between folic acid fortification and cancer.

In October 2009, the SACN announced its decision to support its previous recommendation for mandatory folic acid fortification together with controls on voluntary fortification

Scientific reviews – FFI 2nd Technical Workshop, Stone Mountain, Georgia, 2008

Joint Statement – WHO, FAO, UNICEF, GAIN, MI, FFI

Intention - To set standards for a wide audience including food industry, scientists and governments, involved in the design and implementation of flour fortification programs as public health interventions.

World Health Organization

Recommendations on Wheat and Maize Flour Fortification
Meeting Report: Interim Consensus Statement

Table 1. Average nutrient levels to consider adding to fortified wheat flour based on extraction, fortificant compound, and estimated *per capita* flour availability

Nutrient	Flour Extraction Rate	Compound	Level of nutrient to be added in parts per million (ppm) by estimated average per capita wheat flour availability (g/day)[1]			
			<75[2] g/day	75-149 g/day	150-300 g/day	>300 g/day
Iron	Low	NaFeEDTA	40	40	20	15
		Ferrous Sulfate	60	60	30	20
		Ferrous Fumarate	60	60	30	20
		Electrolytic Iron	NR[3]	NR[3]	60	40
	High	NaFeEDTA	40	40	20	15
Folic acid			5.0	2.6	1.3	1.0
Vit B12			0.04	0.02	0.01	0.008
Vit A	Low or High	Vitamin A Palmitate	5.9	3	1.5	1
Zinc	Low	Zinc Oxide	95	55	40	30
	High	Zinc Oxide	100	100	80	70

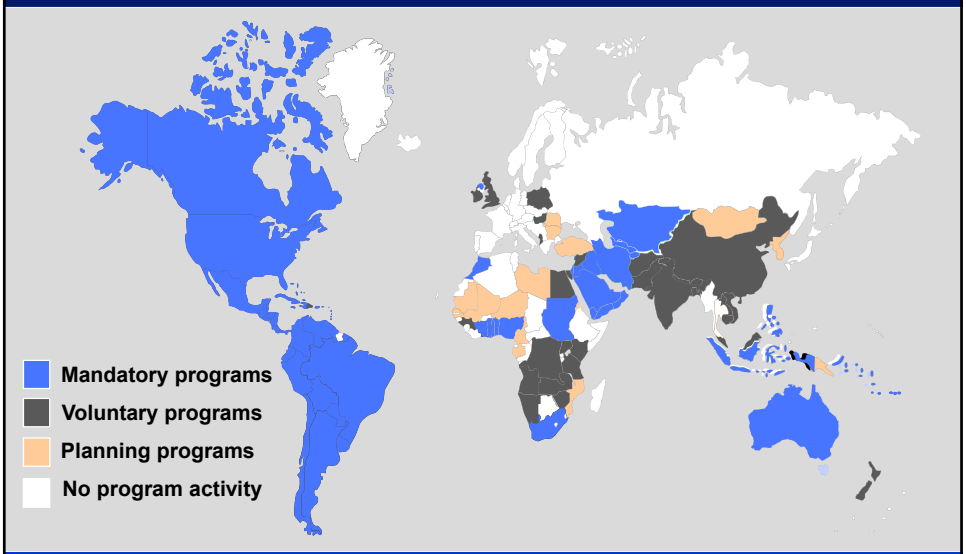
Summary of mandatory fortification with folic acid

- Blood folate levels have increased substantially
- Increased folic acid in fortified flour and foods means decreased numbers of babies born with NTD
- At the present time, there are no proven adverse outcomes of folic acid fortification
  - Very unlikely for usual intake to exceed the UL
  - Very unlikely (alone) to result in high blood folate concentrations
  - Current evidence from research studies shows that few, if any, potential adverse outcomes are associated with folic acid fortification

Summary of mandatory fortification with folic acid (cont'd)

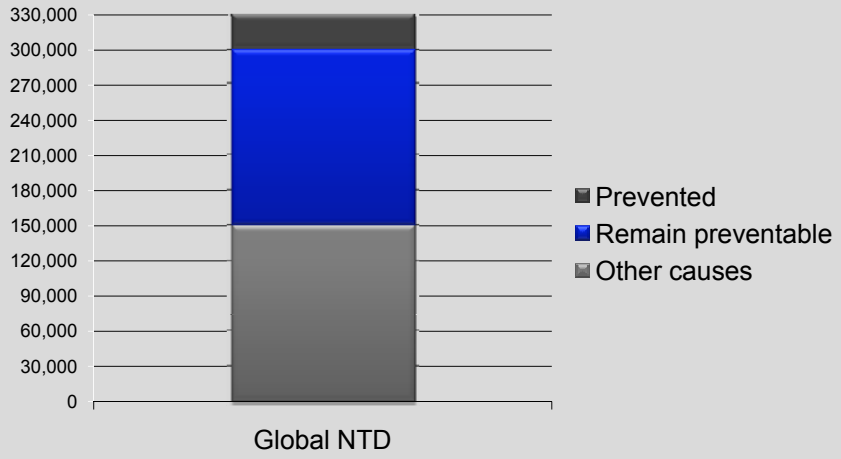
- Current decreases in NTD prevalence do not necessarily reflect the full prevention potential
- Fortification of foods with folic acid is a feasible, economical, safe and effective public health policy.

Worldwide Wheat Flour Fortification Programs



Flour Fortification Initiative website, July 2009

Folic Acid Preventable Neural Tube Defects in 2008



Important activities to facilitate fortification of flour with folic acid

- Improve monitoring of NTDs and other potential adverse health outcomes.
- Provide support for countries preparing to develop plans to fortify flour with folic acid.
- Standardize the measurement of blood folate concentrations for different assays.
- Determine blood folate concentrations associated with lowest prevalence of preventable NTDs.

Acknowledgements

Centers for Disease Control and Prevention

- NCBDDD
  - RJ Berry
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  - Owen Devine
- NCEH
  - Christine Pfeiffer
- NOPHG
  - Quanhe Yang

University of Florida

- Lynn Bailey

Iowa State University

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