IPTV link also available on Grand Rounds intranet site: http://intranet.cdc.gov/od/odweb/about/directorGrandRounds.htm

For those outside of CDC, a broadband link is available at: http://www.cdc.gov/about/grand-rounds (Grand Rounds internet site)
PHGR January 21: 4,404 External Viewers!
Continuing Education Credits

As of January 2010
Credit Hours are available for:

- Physicians (CME)
- Non-Physicians (CME)
- Nurses (CNE)
- Certified Health Education Specialists (CECH)
- Pharmacist (CPE)
- Other Professionals (CEU)

ALL Continuing Education credits/contact hours for PHGR are issued online through the CDC/ATSDR Training & Continuing Education Online system, [http://www2a.cdc.gov/TCEOnline](http://www2a.cdc.gov/TCEOnline).
Selection of NTD and folic acid-related articles: RJ Berry (NCBDDD)

Maternal and Child Health - Folic Acid

70. Central nervous system congenital malformations in a developing country: issues and challenges against their prevention. Adeleye AO, Dairo MD, Olowookere KG. Childs Nerv Syst. 2010 Jan 21. [+]Show Abstract


Stay Tuned

Mar 18  Radiological and Nuclear Preparedness
Apr 15  Preventing Health Effects from Nanotechnology
May 20  Chlamydia Prevention and Control
June 17  Obesity

The Public Health Grand Rounds email address: grandrounds@cdc.gov
Factors that Affect Health

- **Socioeconomic Factors**
  - Poverty, education, housing, inequality

- **Long-lasting Protective Interventions**
  - Changing the Context to make individuals’ default decisions healthy

- **Clinical Interventions**
  - Counseling & Education

- **Examples**
  - Eat healthy, be physically active
  - Rx for high blood pressure, high cholesterol, diabetes
  - Immunizations, brief intervention, cessation treatment, colonoscopy
  - Fluoridation, 0g trans fat, folic acid fortification, iodization, smoke-free laws, tobacco tax
  - Poverty, education, housing, inequality
The Prevention of Neural Tube Defects and Folic Acid Fortification

National Center on Birth Defects and Developmental Disabilities
NCBDDD
Outline

- Joe Mulinare, MD, MSPH
  - Prevention of Neural Tube Defects – the Scope of the Problem

- William Dietz, MD, PhD
  - Global Strategies and Efforts to Reduce the Burden of Neural Tube Defects Worldwide

- Richard B. Johnston, Jr., MD
  - Can Intake of Folic Acid Cause Harm? What Does the Evidence Show?

- Jessica Leighton, PhD, MPH
  - Folic Acid Fortification. Next Steps: Fortification of Corn Masa Flour?
PREVENTION OF NEURAL TUBE DEFECTS - THE SCOPE OF THE PROBLEM

Joe Mulinare MD, MSPH
Prevention Research Team Lead
National Center on Birth Defects and Developmental Disabilities
NCBDDD
Neural tube defects (NTDs)
Evidence-base for folic acid use and prevention of NTDs
Strategies to achieve effective folic acid levels
Impact of folic acid use to reduce the prevalence of NTDs
Existing challenges
- Targeting higher risk populations
- Achieving global efforts of fortification
Neural tube defects (NTDs)

Evidence-base for folic acid use and prevention of NTDs

Strategies to achieve effective folic acid levels

Impact of folic acid use to reduce the prevalence of NTDs

Existing challenges

- Targeting higher risk populations
- Achieving global efforts of fortification
Anencephaly and Spina bifida
Embryo Development 22 - 28 Days of Gestation

Anencephaly

Spina bifida

www.med.unc.edu/embryo_images
Greenwood Genetic Center
Neural Tube Defect Facts

- NTDs develop in 1st month after conception
- >50% of all pregnancies in the United States are unplanned
- Research studies on folic acid have shown that 50% to 70% of NTDs are preventable
- To prevent NTDs, it is recommended that all women capable of becoming pregnant consume at least 400 µg folic acid daily
Before folic acid fortification of cereal grain products, there were about 4,000 pregnancies with NTDs/year.

Since fortification began in January 1998, that number has decreased to about 3,000 affected pregnancies.

Since fortification began, NTDs have been prevented in more than 12,000 babies.

States with NTD surveillance programs
Neural Tube Defect Surveillance Worldwide 2006

PREVENTION OF NEURAL TUBE DEFECTS -
THE SCOPE OF THE PROBLEM

- Neural tube defects (NTDs)
- Evidence-base for folic acid use and prevention of NTDs
- Strategies to achieve effective folic acid levels
- Impact of folic acid use to reduce the prevalence of NTDs
- Existing challenges
  - Targeting higher risk populations
  - Achieving global efforts of fortification
What Is Folate or Folic Acid?

- Folate is generic term for 2 different forms of vitamin B9
  - Naturally occurring food folate - polyglutamate form
    - Legumes, beef liver, green leafy vegetables, some fruits, whole grains
  - Synthetic folic acid - monoglutamate form
    - Enriched cereal grain products - breads, pasta, rice, etc.
    - Ready-to-eat cereals
    - Supplements

- Folic acid is about 2x more bioavailable than food folate
### Scientific Evidence for Prevention of NTDs
#### NTD Studies, 1980-1999

<table>
<thead>
<tr>
<th>Studies</th>
<th>Percentage NTD Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980 – England</td>
<td>86%</td>
</tr>
<tr>
<td>1981 – S. Wales</td>
<td>59%</td>
</tr>
<tr>
<td>1988 – Atlanta</td>
<td>60%</td>
</tr>
<tr>
<td>1989 – W. Australia</td>
<td>70%</td>
</tr>
<tr>
<td>1989 – California / Illinois</td>
<td>7%</td>
</tr>
<tr>
<td>1989 – Boston</td>
<td>65%</td>
</tr>
<tr>
<td>1990 – Cuba</td>
<td>100%</td>
</tr>
<tr>
<td>1991 – UK and Other Countries</td>
<td>71%</td>
</tr>
<tr>
<td>1992 – Hungary</td>
<td>100%</td>
</tr>
<tr>
<td>1993 – New England</td>
<td>60%</td>
</tr>
<tr>
<td>1995 – Ireland</td>
<td>80%</td>
</tr>
<tr>
<td>1999 – China</td>
<td>79%</td>
</tr>
</tbody>
</table>
Periconceptional Folic Acid Community Trial to Prevent NTDs, China, 1993 – 1996

Intervention = 400 µg Daily Folic Acid Supplement Alone

- No folic acid: NTDs per 10,000 pregnancies
  - North: 7
  - South: 10
- Folic acid: NTDs per 10,000 pregnancies
  - North: 6
  - South: 10

85% reduction in NTDs in the North compared to the South.
PREVENTION OF NEURAL TUBE DEFECTS - THE SCOPE OF THE PROBLEM

- Neural tube defects (NTDs)
- Evidence-base for folic acid use and prevention of NTDs
- Strategies to achieve effective folic acid levels
- Impact of folic acid use to reduce the prevalence of NTDs
- Existing challenges
  - Targeting higher risk populations
  - Achieving global efforts of fortification
Approaches to Increase Folate/Folic Acid Intake

Diet...natural foods, vegetables, fruits, beans, yeast, liver

Pills... folic acid-containing dietary supplements

Fortification... folic acid added to foods - flour, rice, pasta, breakfast cereals

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
## Folic Acid and Dietary Folate Consumption Study
### Mean Red Cell Folate Results, Ireland 1996

<table>
<thead>
<tr>
<th>Intervention Approach</th>
<th>Mean Red Blood Cell Folate Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>+ 5%</td>
</tr>
<tr>
<td>Dietary Advice</td>
<td>+16%</td>
</tr>
<tr>
<td>Dietary Food Folates 400 µg Folate</td>
<td>+11%</td>
</tr>
<tr>
<td>Supplements 400 µg Folic Acid</td>
<td>+40%</td>
</tr>
<tr>
<td>Fortified Foods 400 µg Folic Acid</td>
<td>+52%</td>
</tr>
</tbody>
</table>

Cuskelley et al., Lancet; 1996.
Science-based Policy-making: USPHS, IOM, and FDA
Folic Acid and Neural Tube Prevention

- 1992 - US Public Health Service recommendation: improve dietary habits, take a daily folic acid supplement, consume folic acid-fortified foods
- 1996 - FDA regulation: all enriched cereal grain flour and products must be fortified with folic acid (140 µg/100g)
- 1998 - Institute of Medicine recommendation: 400 µg folic acid from fortified foods, supplements, or both in addition to consuming food folate from a varied diet
PREVENTION OF NEURAL TUBE DEFECTS - THE SCOPE OF THE PROBLEM

- Neural tube defects (NTDs)
- Evidence-base for folic acid use and prevention of NTDs
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  - Targeting higher risk populations
  - Achieving global efforts of fortification
Serum Folate Concentrations ($\geq 20$ ng/mL) Before and After Fortification
Kaiser Permanente Southern California, 1994-2001

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Lawrence JM, Chiu V, Petitti DB. NEJM 2000; 343: 970.
Data for 2000 and 2001 added since publication. Data for 2001 is Jan-Sep, 2001. (12/4/01)
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Before and After Fortification
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Data for 2000 and 2001 added since publication Data for 2001 is Jan-Sep, 2001. (12/4/01)
NTD Prevalence by Fortification Status
25 States, National Birth Defects Prevention Network
1995-2006

Prevalence per 10,000 births

Year


Pre - fortification  Optional fortification  Mandatory fortification

26%↓  37%↓
Economic Evaluation of Folic Acid Fortification in the United States

- Through 2006, 37% reduction in NTDs
- Program costs
  - Fortification of flour: $3 million/year
  - Direct cost averted: $145 million/year
  - For every $1 invested there are >$45 in medical costs averted/year
- Lifetime medical costs per child with spina bifida are $461,000

Grosse et al. AJPH 2005
PREVENTION OF NEURAL TUBE DEFECTS - THE SCOPE OF THE PROBLEM

- Neural tube defects (NTDs)
- Evidence-base for folic acid use and prevention of NTDs
- Strategies to achieve effective folic acid levels
- Impact of folic acid use to reduce the prevalence of NTDs

- Existing challenges
  - Targeting higher risk populations
  - Achieving global efforts of fortification
Neural Tube Defects
Other Risk Factors: 5%-10%

- Previous NTD-affected pregnancy
- Genetic variants
- Maternal diabetes
- Obesity
- Hyperthermia, fever
- Antiepileptic medications
- Lower socioeconomic status
- Race/ethnicity: Hispanic > white > black
NTD Prevalence by Race, 25 States
National Birth Defects Prevention Network
1995 - 2006

Prevalence per 10,000 births

Year

Pre - fortification
Optional fortification
Mandatory fortification

Hispanic
White
Black

Support for concept of fortified corn masa flour

Partners
- National Council of La Raza
- Wal-Mart Stores
- Spina Bifida Association
- Local and state partners

Gruma, largest producer of corn masa flour in the United States expressed interest in fortification
## Folic Acid Intake from Supplements and Corn Masa Flour

**Women 15-44 yrs, NHANES 2001-2004**

<table>
<thead>
<tr>
<th></th>
<th>Supplements</th>
<th>Corn Masa Flour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White Non-Hispanic</strong></td>
<td>37%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Black Non-Hispanic</strong></td>
<td>15%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Mexican-American</strong></td>
<td>21%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Hamner H, AJCN 2009, Table 1

NH, non-Hispanic
Total Usual Daily Folic Acid Intakes Without (Actual) and With (Modeled) Folic Acid Fortification of Corn Masa Flour
Women 15-44 yrs, by Race/Ethnicity

Hamner H, AJCN 2009, Table 2
NH, non-Hispanic
Worldwide Wheat Flour Fortification Programs

Flour Fortification Initiative website, July 2009
Global NTD Rate Changes
Before and After Folic Acid Fortification

NTDs per 10,000 live births

-37% 10.8 6.6 8.6 9.7 6.3 10.1 14.1 9.8
-46% 15.8 15.8 9.7 6.3 10.1 17.0 14.1 9.8
-35% 10.1 10.1 6.3 9.7 6.3 9.7 10.1 9.8
-41% 17.0 17.0 10.1 10.1 10.1 17.0 14.1 14.1
-31% 14.1 14.1 10.1 10.1 10.1 17.0 14.1 14.1

Before fortification
After fortification
Summary/Conclusions

- NTDs are life-threatening and cause life-long disabilities
- 50%-70% of NTDs can be prevented with 400 µg folic acid daily
- Fortification of foods with folic acid is a feasible, economical, safe, and effective public health policy to prevent neural tube defects worldwide
Remaining Challenges and Questions

How will we know when we have eliminated all folic acid-preventable NTDs?

- When all women reach a specified consumption or blood level?
- When NTD rates stabilize at some specified level?
- When we understand the underlying biology of NTD prevention?
Proposed Future Activities

Global Focus

- **Partnerships**: Strengthen global partnerships to support mandatory folic acid fortification policies and programs

- **Monitoring and Evaluation**: Develop and improve surveillance and evaluation systems to assess program effectiveness

- **Communication**: Promote and sustain mandatory fortification programs

- **Research**: Expand science base for global mandatory folic acid fortification, include evaluation of studies related to adverse effects
GLOBAL STRATEGIES AND EFFORTS TO REDUCE THE BURDEN OF NEURAL TUBE DEFECTS WORLDWIDE

William Dietz, MD, PhD
Director
Division of Nutrition, Physical Activity, and Obesity
National Center for Chronic Disease Prevention and Health Promotion
Annual Burden Worldwide from Micronutrient Deficiencies

- 18,000,000 babies are born with impaired mental development due to iodine deficiency
- 1,100,000 children <5 years old die due to Vitamin A and Zn deficiency
- 350,000 children become blind due to Vitamin A deficiency
- 300,000 children are born with NTDs due to folic acid insufficiency
- 115,000 maternal deaths (20%) are associated with iron deficiency
Folic Acid Preventable Neural Tube Defects in 2008
The 2008 Copenhagen Consensus concluded that nutrition interventions are 5 of the top 10 most cost-effective means to address global morbidity and mortality challenges.

More than 400 million tons of wheat is milled for human consumption every year.

(Food and Agriculture Organization of the United Nations)
Feasibility of Flour Fortification

- Technology: simple and well established
- Economical: premix cost of adding iron and folic acid to flour
  - Ferrous sulfate and folic acid: $0.85-$1.10/metric ton of flour
Recommendations and Wheat Flour Consumption

- **WHO recommendations on wheat and maize flour fortification:**
  Fortification likely to have an impact in countries where average flour consumption is \( \geq 75 \text{ g/person/day} \)

- **Wheat flour consumption:** 80% of the world’s population consumes on average \( \geq 75 \text{ g/person/day} \)

Economic Evaluation of Folic Acid Fortification in Chile

- In 1998 Chile fortified wheat flour at 220 µg /100g flour
- Reduction in NTDs (thru 2001): 41%
- Cost of fortification: $0.2 million/ year ($1)
- Direct cost averted: $2.2 million/ year ($11)
Flour Fortification Initiative (FFI)

FFI includes:
- Cargill
- Buhler
- Millers’ organizations

Sectors involved:
- Private Sector
- Public Sector
- Civic Sector

Partners:
- WHO
- UNICEF
- GAIN
Flour Fortification Progress Since 2004

- Growth in fortified flour from mills increased from 18% to 30%

- Nearly 2 billion people now have potential access to fortified flour - 858 million more than in 2004

- The number of countries with documented national regulations for mandatory wheat flour fortification increased from 33 to 58 (51 fortify with folic acid)

- Regulation does not imply compliance
Challenges to Mandatory Flour Fortification

- Need for regulatory framework
- Large mills vs small mills
- Acceptance
- How to reach large population countries (China, India)
- Impact of fortification on NTDs in developing countries
CAN INTAKE OF FOLIC ACID CAUSE HARM? WHAT DOES THE EVIDENCE SHOW?

Richard B. Johnston, Jr., MD
Professor of Pediatrics, Associate Dean for Research Development
University of Colorado School of Medicine
Potential Adverse Effects of Folic Acid: Concerns and Evidence

- Progression of nerve damage in B12-deficient patients
- Excess intake in children
- Unmetabolized folic acid
- Blunting of antifolate therapy
  - Methotrexate and phenytoin
- Twinning and miscarriages
- Cognitive decline
- Epigenetic hypermethylation
- Cancer promotion
Progression of Nerve Damage in B12-Deficient Patients

- Case reports, 1940s-50s: Folic acid doses of >5000 µg could eliminate the anemia of pernicious anemia while allowing neurologic damage to proceed.
- IOM adopted 5000 µg as lowest observed adverse effect level to derive tolerable upper intake level of 1000 µg/day.
- NHANES data 2003-06: 2.7% of U.S. adult population exceeded 1000 µg/day intake; only those who consumed >400 µg/day as supplement exceeded the upper level.
- Conclusion: No known evidence that folic acid at current intake levels has masked B12 deficiency or harmed individuals with B12-deficiency or pernicious anemia.

IOM, Institute of Medicine
Excess Intake in Children

- In absence of evidence of direct toxic effects of folic acid at any dose, any identified risk to children, and data on utilization and turnover in children, the IOM adjusted down upper intake level from 1000 µg/day on basis of relative body weight

- **Conclusion:** No known evidence that folic acid intake above IOM-recommended levels has harmed children. Considering the rapid growth that characterizes childhood, it is possible that relatively higher doses of folic acid are beneficial
Unmetabolized Folic Acid

- Folic acid is converted to active form in tissues; excess folic acid enters the circulation and is excreted
- Circulating unmetabolized folic acid has been reported after intake of as little as 300 µg in bolus
- Surveys since 1980: ~25% of U.S. adults take folic acid in supplement form; most pregnant women take 600-800 µg/day in prenatal supplement
- **Conclusion:** Adult and newborn Americans have been exposed to unmetabolized folic acid for decades; no harm has been detected
Blunting of Anti-Folate Therapy: Methotrexate and Phenytoin

- Concern raised that more folic acid intake could interfere with methotrexate therapy (cancer, inflammation) or phenytoin treatment (seizures)
- According to standards of care, both agents are used over wide dose ranges, and dosage is tailored to each individual to optimize benefit and avoid toxicity; folate supplement (commonly 1000 µg/day) is given routinely with methotrexate
- **Conclusion**: No known evidence that folic acid intake has interfered with standard antifolate therapy
Twinning and Miscarriages

- Early studies suggested periconceptional vitamin use was associated with more multiple births and miscarriages, but confounding variables were not excluded.
- Low blood folate levels, but not high levels, have been associated with increased miscarriages.
- Twinning rates not affected by:
  - Folic acid fortification in United States
  - 400 µg/day folic acid supplement in China trial
  - Higher blood folate levels
- **Conclusion:** No known evidence to indicate that increased folic acid intake increases multiple births or miscarriages.
Cognitive Decline

- Elevated blood homocysteine levels, low blood folate levels, or low folate intake have been associated with increased rates of dementia in most studies, including randomized controlled trials, but not in all.

- Patients with low blood B12 levels but relatively high blood folate levels scored more poorly on memory tests:
  - Due to folic acid interference with B12 metabolism in some way?
  - Due to preclinical pernicious anemia in supplement takers who absorb folates but not B12?

- 97% of those with normal B12 and high blood folate levels had evidence of increased cognition.

- Conclusion: There is no evidence of harm and some evidence of benefit, but data are conflicting.
Folates are potent source of methyl groups. Could higher folic acid intake increase methylation of DNA residues that influence development of tumors or other disease?

- Pregnant mice fed high doses of 4 methyl donors delivered offspring with hypermethylation of coat-color gene and change in coat color of newborns
- Humans given 5000-10,000 µg/day folic acid for 3-12 months had increased DNA methylation in resected colorectal adenomas; but 2000 µg/day for 6 months did not modify lymphocyte DNA

**Conclusion:** No evidence of harm to date, but epigenetic methylation is biologically plausible; further research is needed
Cancer Promotion

- Higher folate status has been associated with relative protection against several cancers.
- Periconceptional folic acid supplement and fortification have been associated with reduced risk of 3 childhood cancers.
- Mice bred to develop colorectal adenomas:
  - High-dose folic acid decreased adenomas if given before adenoma formation.
  - But increased adenomas if given after adenoma formation had begun.
- Humans with prior adenoma given 1000 µg/day folic acid for 3-5 years had increased risk of recurrence of ≥ 3 adenomas.

Conclusion: No evidence of harm at intakes recommended to prevent NTDs; possible risk of cancer at high doses in supplement takers; more research is needed.
Summary and Recommendations

- No data exist to indicate that intake of folic acid causes harm
  - At levels in fortified foods
  - At levels recommended to prevent NTDs
  - But data not yet clear with intake of supplements of >400 µg/day

- Folic acid doses at recommended levels probably prevent occurrence of cancer; but folic acid at higher doses could promote growth of existing malignancy

- Continued monitoring and research are clearly needed to avoid the potential of harm in any form

- Should be emphasized that prevention of NTDs by periconceptional folic acid is accepted as proven

- And an estimated 150,000 NTDs/year could be prevented worldwide by adequate fortification of foods with folic acid
FOLIC ACID FORTIFICATION. NEXT STEPS: FORTIFICATION OF CORN MASA FLOUR?

Jessica Leighton, PhD, MPH
Senior Advisor for Science
Office of the Commissioner, Office of Foods, FDA
Regulation of Folic Acid Fortification

- Manufacturers cannot arbitrarily add folic acid to foods

- Regulations allow folic acid fortification by
  - Food Standards (Standard of Identity): e.g., enriched cereal grain product
  - Food Additives (folic acid added to enriched cereal products)
Folic Acid Fortification

- **1941 standard of identity established for “enriched” flour**
  - Flour is not required to be enriched, but if claimed to be enriched, had to contain thiamin, riboflavin, niacin, iron

- **Regulation Approved 1996; Effective January 1998**
  - Mandated folic acid in “enriched” cereal grain products that conformed to a standard of identity
  - Allowed the fortification of breakfast cereals and dietary supplements
Fortification Considerations

- Documentation of public health need
- Implementation issues
- Safety issues
- Monitoring and enforcement issues
Fortification Considerations

- Documentation of public health need
- Implementation issues
- Safety issues
- Monitoring and enforcement issues
Folic acid fortification of enriched cereal products has had a substantial impact in reducing NTDs

Disparity: Hispanic women have 20% higher risk of a NTD-affected pregnancy

How much more folic acid should be added
Dramatic Decline in Prevalence of Low Blood Folate Concentrations and Spina Bifida

Percent RBC below 140 ng/mL

- N-H black
- Hispanics
- N-H white

Prevalence of spina bifida /10,000 births

Early post fortification (1999-2000)
Post fortification (2001-2002)
Post fortification (2003-2004)
Post fortification (2005-2006)
Fortification Considerations

- Documentation of public health need
- Implementation issues
- Safety issues
- Monitoring and enforcement issues
Implementation Issue
What Additional Foods Could be Fortified?

- Proposal by industry, advocacy groups, CDC to fortify corn masa flour
- Products containing corn masa flour are more likely consumed by Mexican Americans than other U.S. populations
- Corn masa flour is prepared from corn boiled in an alkaline lime water solution
- Found in many types of food
  - Corn tortillas, taco shell, corn and tortilla chips, tamales, enchiladas, chalupas
- No existing federal regulations that permit folic acid fortification of corn masa flour
Implementation Issue

How much?

- How much should be added to achieve the final level desired considering natural levels in the corn masa flour and the potential stability issues?
Implementation Issue: Consumer Acceptance

How does fortification affect physical characteristics?
- Taste
- Color
- Texture

Cultural issues must also be considered

Lessons learned from wheat flour can be informative but still need independent assessment for corn masa flour
Fortification Considerations

- Documentation of public health need
- Implementation issues
- Safety issues
- Monitoring and enforcement issues
Safety Issues

- Safety is critical
- Food additive regulations do not consider risk benefit. They only consider safety issues.
  - Rather, there must be evidence of reasonable certainty of no harm
Fortification Considerations

- Documentation of public health need
- Implementation issues
- Safety issues
- Monitoring and enforcement issues
Monitoring

- **Effectiveness**
  - Folic acid intake from all sources
  - Blood folate concentrations
  - Neural tube defects

- **Safety**
  - Monitor potential for potential adverse effects

- **Validated methods to analyze the manufactured and finished products**
Safety assessments and food technology issues are key information needed

- First, need to demonstrate safety under requirements of reasonable certainty of no harm
- Documentation of public health need
- Amount of additive proposed for use
- Description of methods to determine amount of food additive in raw, processed or finished food
Corn Masa Fortification?
Other Issues

- **Implementation Issues**
  - Determine the stability and shelf life of folic acid added to corn masa flour
  - Assess any acceptance issues

- **Availability of validated methods for analysis of folic acid in fortified products and standards for**
  - Industry to ensure product content and labeling accuracy
  - FDA in its enforcement role
Fortification of enriched flour with folic acid has been a public health success story in improving blood folate concentrations and reducing NTDs.

NTDs continue to affect thousands of Americans and disparities exist.

Fortification of additional foods with folic acid may reduce the disparities.
Next Steps

- Collaboration is essential and requires
  - Defined roles of industry, academia, CDC, NIH, FDA, and others
  - Public health consensus on solutions and safety
  - Food technology research (stability, shelf live and analytic methodologies)
  - Regulatory process
Mean Folic Acid Intake, Enriched Cereal-Grain Products, RTE Cereals & Supplements by Serum Folate Quintiles
NHANES 2001-2004, ≥19 years, n=8,655

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