



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

AUG 14 2000

Food and Drug Administration  
Washington DC 20204

George K. Anderson, MD, MPH, FACPM  
President  
American College of Preventive Medicine  
1660 L Street, N.W.  
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Washington, D.C. 20036-5603

Dear Dr. Anderson:

This responds to your letter of March 7, 2000, urging the Food and Drug Administration to re-examine its folic acid food fortification policy and to increase the current level of folic acid fortification of enriched cereal grain products to 350 micrograms per 100 grams. We commend the continued support by the American College of Preventive Medicine (ACPM) of a policy for folic acid fortification of enriched foods to reduce the occurrence of neural tube birth defects. However, we do not agree that changing the level of folic acid fortification of enriched grain products is warranted at this time.

Considerable deliberation was involved in FDA's development of its folate fortification policy. The agency summarized the many uncertainties related to folate fortification, including those related to effective dose and safety of fortification for the general population, in its Federal Register documents of October 14, 1993, and March 5, 1996.

Currently, FDA and other federal agencies are actively working to assess the effects of the fortification program. Such an assessment must precede a discussion of whether the current fortification program should be changed. Ongoing measurement of changes in the prevalence of neural tube birth defects in the U.S. will enable the effectiveness of folate fortification to be evaluated. Other approaches are also being used to estimate the effects of fortification. These include measurement of the effects of short-term feeding of fortified foods on indices of folate status, measurement of indices of folate status in individuals before and after implementation of the fortification program, and estimation of current folate intakes based upon updated food consumption surveys and food composition data bases. For example, several recent reports have shown significant increases in plasma folate values following the initiation of fortification

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(Jacques, et al. <sup>1</sup>, Lawrence, et al. <sup>2</sup>). Additional data should be available in the next few months.

Pending critical evaluation of the emerging data on the impact of the current folate fortification program, it is premature to change fortification levels at this time. However, FDA is actively consulting with other federal government public health agencies on this important public health policy issue. As warranted by new evidence, the agency will consider adjustments to the fortification requirements.

Sincerely,

*for Janice F. Oliver*  
Joseph A. Levitt  
Director  
Center for Food Safety  
and Applied Nutrition

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<sup>1</sup> P.F. Jacques, J. Selhub, A.G. Bostom, P.W.F. Wilson, and I.H. Rosenberg (1999). The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *The New England Journal of Medicine*. 340:1449- 1454.

<sup>2</sup> J.M. Lawrence, D.B. Petitti, M. Watkins, and M.A. Umekubo (1999). Trends in serum folate after food fortification. *The Lancet*. 354:915-916.

***Leadership in the Science, Policy and Practice of Preventive Medicine***

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March 7, 2000

Joseph A. Levitt  
Director  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
Department of Health and Human Services  
5600 Fishers Lane  
Rockville, MD 20857

Dear Mr. Levitt:

Thank you for your response to the American College of Preventive Medicine's letter on folic acid fortification of the U.S. food supply to prevent neural tube defects (*see attached letter*).

In your response to ACPM's letter, you explained that a folic acid fortification program must assure the safety of the fortification level not only for child-bearing women, but for the entire U.S. population. The FDA believes additional post-fortification monitoring data both of child-bearing women and other populations is necessary before altering the current fortification level. ACPM feels, however, that the evidence currently exists to support an increase in the standard fortification level to 350 micrograms.

In its previously-submitted public policy statement on folic acid fortification, ACPM addresses the impact of reducing neural tube defects through a population-based approach (*see attached policy statement*). It recognizes the potential adverse health outcomes and economic considerations of fortification, particularly those associated with neurologic complications resulting from delayed diagnoses of B-12 deficiency anemia. However, ACPM also identifies benefits of additional folic acid fortification for certain populations other than child-bearing women, as specified in the ACPM policy statement.

Based on an analysis of the existing literature, ACPM continues to support a fortification policy of enriched foods with folic acid to reduce the occurrence of neural tube defects. While the highest level, 700 micrograms, may prevent the most defects and be the most cost-effective, this level of fortification runs the highest risk of causing harm to other population groups. A level of 140 micrograms is the least cost-effective compared to the higher alternatives and prevents substantially fewer neural tube defects. Thus, at this

Letter to Joseph Levitt

03/07/00

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time a level of at least 350 micrograms appears to be the most appropriate fortification level to maximize the prevention of neural tube defects, while protecting the health of the general population. ACPM urges the FDA to re-examine its 1996 policy in light of more recent findings.

We appreciate your attention to this issue. Please do not hesitate to contact ACPM at 202-466-2662 if we can be of further assistance.

Sincerely,

A handwritten signature in cursive script that reads "George K. Anderson".

George K. Anderson, MD, MPH, FACPM  
President

Enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Washington, DC 20204

SEP 28 1999

George K. Anderson, M.D.  
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Dear Dr. Anderson:

Thank you for your letter and the American College of Preventive Medicine public policy statement on folic acid fortification of the U.S. food supply to prevent neural tube defects. Because the Center for Food Safety and Applied Nutrition is responsible for the folic acid fortification program, Dr. Henney referred your letter to this center for reply.

As you know, mandatory folic acid fortification of enriched cereal grain products became fully effective in January, 1998. While the fortification program was implemented with the primary objective of lowering the risk of neural tube defects, it must also assure the safety of the fortification level for the entire U.S. population. FDA, in conjunction with other Public Health Service agencies, is currently monitoring the safety and effectiveness of this program.

Fortification of the U.S. food supply always requires a balance between achieving effective intakes for the target population and avoiding undue risk for non-target persons because of potentially high intakes. Few data relevant for fortification decisions make it difficult to define this point precisely. Therefore, in all fortification programs, post-fortification monitoring data are critical to evaluate the safety and effectiveness of these programs. If significant and compelling new data become available to suggest that changes in the fortification program are needed, FDA can initiate steps needed to amend its regulations.

At this time, FDA believes that it is premature to suggest changes in the current folic acid fortification program based on available data, including results from new studies and previous experience with national food fortification programs; however, we will continue to monitor the impact of folic acid fortification and make changes as new evidence warrants.

Sincerely yours,

A handwritten signature in cursive script that reads "Joseph A. Levitt".

Joseph A. Levitt.  
Director  
Center for Food Safety  
and Applied Nutrition

# American College of Preventive Medicine Public Policy Statement Folic Acid Fortification of Grain Products in the U.S. to Prevent Neural Tube Defects

Jennifer R. Bentley, MD, MPH, Rebecca L. Ferrini, MD, MPH, Linda L. Hill, MD, MPH

Based on a review of current literature and recommendations, the American College of Preventive Medicine presents a public policy statement on folic acid fortification.

**Medical Subject Headings (MeSH):** community health centers, community health planning, interinstitutional relations, public health, folic acid, folic acid deficiency, neural tube defects, grain; food, fortified. (Am J Prev Med 1999;16(3):264-267) © 1999 American Journal of Preventive Medicine

## Burden of Suffering

Neural tube defects (NTD), specifically spina bifida and anencephaly, affect approximately 4,000 live births and pregnancies each year in the United States.<sup>1</sup> Of these, the Centers for Disease Control and Prevention (CDC) report that 1500 infants are born with spina bifida, 1000 are born with anencephaly, and an estimated 1500 fetuses are aborted annually.<sup>2</sup> NTDs are implicated in 1.3% of all infant deaths and are second only to cardiac defects as the leading cause of perinatal mortality from all birth defects.<sup>3</sup> These spinal cord malformations are associated with serious developmental disabilities including muscle weakness and/or paralysis, bowel and bladder incontinence, and intellectual impairment. While infants with anencephaly usually die shortly after birth, those with spina bifida usually survive into adulthood. The combined lifetime medical and indirect costs for a survivor with spina bifida are estimated to be \$350,000.<sup>4</sup> For all those affected, the total annual economic burden is in excess of \$480 million.<sup>5</sup>

Certain maternal factors are associated with an increased risk of neural tube defects, including previous history of NTD-affected pregnancy (20-30-fold elevation in risk), genetic defects in folate metabolism, and reduced periconceptional intake of folic acid. The incidence of NTDs has decreased since the 1930s (5 per 1000 to less than 5 per 10,000 live births).<sup>6</sup> This has been attributed to prenatal diagnosis with selective

pregnancy termination and nutritional factors. Inadequate dietary intake of folic acid has been implicated as a substantive, if not primary, cause of NTDs.<sup>7</sup> The CDC estimates that 50%-70% of NTDs could be prevented if women consumed at least 400 micrograms of folic acid daily.<sup>7</sup>

Unfortunately, recent nutritional surveys demonstrate that, on average, U.S. women of childbearing age consume only about half of the 400 micrograms of folate recommended.<sup>8</sup> In a 1997 March of Dimes Birth Defects Foundation, survey only 66% of women reported ever hearing about folic acid; only 16% reported knowledge that it helps reduce birth defects; and only 9% reported knowledge that it should be taken before pregnancy.<sup>2</sup> Overall, as few as 30% of non-pregnant women of childbearing age reported taking a vitamin supplement containing folic acid.<sup>2</sup> Because adequate folic acid levels are required during the first 28 to 30 days of gestation—prior to closure of the neural tube—it is often too late to begin vitamin supplementation once pregnancy is confirmed. Furthermore, in the U.S., about half of all pregnancies are unplanned and many women remain unaware of their pregnancies for several weeks.<sup>9</sup>

## Description of Preventive Measures

To reduce the risk of NTDs, the U.S. Food and Drug Administration (FDA) announced in March 1996 that the U.S. food supply would be fortified with folic acid. The agency mandated that enriched grain products be fortified with 140 micrograms of folic acid per 100 grams of product beginning January 1998.<sup>10</sup> These enriched products include cereal grains and pastas (e.g., macaroni, rice, corn meal, flour, farina, breads, and rolls). This policy statement will examine the

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effectiveness of a fortification program and not discuss alternatives such as physician recommendation of dietary change or folate supplementation or national education campaigns aimed at increasing folate consumption in women of childbearing age.

### **Evidence of Effectiveness**

Over the past 30 years, multiple studies conducted worldwide on diverse populations have shown that there is a reduced risk of neural tube defects in the babies of women who use folic acid supplements. In women with previous NTD-affected pregnancies, two randomized trials and one nonrandomized controlled trial demonstrated significant reductions in NTDs in those who consumed folic acid supplements.<sup>11-13</sup> Additionally, statistically significant reductions in the incidence of first occurrence NTDs were shown in two case-control and two prospective studies in women who received folic acid supplements (100-1000 micrograms) prior to conception and during early pregnancy.<sup>14-17</sup> The effect size in these studies ranged from approximately a 30% reduction in risk to 100%.<sup>7</sup> In one observational study it was dietary folate but not consumption of supplements that had a protective effect on risk of NTD.<sup>18</sup> While one of these studies also showed a dose-response relationship between total dietary folate intake and reduced risk for NTDs, the outcome did not reach statistical significance.<sup>15</sup> However, a few studies failed to report significant reductions in NTDs in users of folate supplements.<sup>19-21</sup>

Based on these studies, experts from the CDC, FDA, Health Resources and Services Administration, and National Institutes of Health estimate folate supplementation of at least 400 micrograms per day can reduce the risk of first occurrence of NTDs by at least 50%.<sup>6</sup> Since it is not known which women are at risk of bearing pregnancies complicated by NTD, it is suggested that all women of childbearing age consume at least this amount of folate daily.

Fortification as an intervention to improve the nation's health has a history of effectiveness in raising dietary nutrient intakes and reducing deficiency diseases; fortification of milk with vitamin D successfully reduced the incidence of rickets, and salt fortification with iodine reduced prevalence of endemic goiter. In the 1940s, niacin, thiamine, and riboflavin were added to cereal grains to replace nutrients lost in the milling process. Therefore, fortifying cereal and other grains, foods reportedly consumed by 90% of women of childbearing age, is an intervention with precedent.<sup>22</sup> The 140-microgram fortification level is estimated to increase a woman's consumption of folic acid by an average of 100 micrograms per day, for a total intake of approximately 300 micrograms.<sup>23</sup>

The greatest hazard associated with folic acid fortification is possible delayed or missed diagnosis of ane-

mia. Folate intake of greater than 1 milligram per day has the potential to mask the megaloblastic anemia produced by vitamin B-12 deficiency, a disease with prevalence estimates between 9 and 28/100,000.<sup>24,25</sup> If untreated, irreversible neurologic problems (numbness, loss of balance, weakness, and paralysis) may result in those patients with this type of anemia. The FDA subcommittee speculated those most at risk for such hematologic disorders, and their subsequent masking, would be those individuals over 50 years of age who are in the 95<sup>th</sup> percentile of folate intakes and also use oral folic acid supplements. This committee estimated the mean daily intakes for these individuals to be 840 micrograms with a 140-microgram fortification and as high as 1.22 milligrams with a 350-microgram fortification.<sup>10</sup>

### **Public Policy Considerations**

In general, folate fortification does not affect the appearance, taste, or shelf life of grain or cereal products. Additional equipment is not required since manufacturers already incorporate the required machinery to produce fortified foods. Also, folate has negligible drug interactions.

However, this population-based approach to reduce the incidence of NTDs would also affect individuals outside of the target population. Adverse health outcomes and economic considerations of fortification are associated primarily with the neurologic complications resulting from delayed diagnoses of B-12 deficiency anemia. Disagreement over the numbers of people likely to be affected by this type of anemia (prevalence studies are limited) makes it difficult to predict these health costs. On the other hand, fortification may have added benefits for certain populations. Lack of this vitamin is one of the most common causes of anemia in the U.S., especially among the elderly and those of lower socioeconomic status.<sup>26,27</sup> Intake of folic acid may mitigate or even prevent vascular disease for some individuals. Supplementation with folic acid can reduce circulating homocysteine. High serum homocysteine levels appear to be an independent risk factor for cardiovascular disease and may be implicated in up to 10% of all coronary artery disease.<sup>28-30</sup> Folic acid intake has also been linked to a reduced risk for cervical dysplasia in women.<sup>31</sup>

Comprehensive cost-effectiveness analyses of a fortification program have been performed by experts in public health. The analyses balance the savings from NTD prevention with the costs of production of fortified foods and neurologic complications of B-12 deficiency. An analysis by Romano et al used the human capital approach and included indirect costs (e.g., productivity losses for those with spina bifida) in the total savings. This report found net benefits of \$94

million with a 140-microgram fortification and \$252 million with a 350-microgram fortification program.<sup>4</sup>

The U.S. Public Health Service directed a panel to compare the cost-effectiveness of three different levels of folate fortification. Life years gained (reduction in premature mortality and morbidity) and cost savings due to prevention of NTDs (including caregiver costs) were used to measure outcomes of effectiveness for each level of fortification compared to no fortification program. The total cost of fortification included production costs and medical costs associated with B-12 deficiency-related neurologic complications. They report 89, and 555, and 1403 fewer NTDs resulting from a 140-microgram, 350-microgram, and 700-microgram fortification program, respectively.<sup>25</sup> Increasing fortification levels also translated into increased numbers of B-12 deficiency-related neurologic complications: 89, 473, and 1388 with a 140-microgram, 350-microgram, and 700-microgram fortification, respectively.<sup>25</sup> This panel reported a total cost savings of \$15 million with a 140-microgram, \$98 million with a 350-microgram, and \$248 million with a 700-microgram fortification program.

In summary, there are reduced health costs for all outcomes with a fortification program compared to no program. Both analyses find the savings driven by the reduction in the number of NTD births. The FDA chose the 140-microgram fortification level primarily because of safety concerns for an unknown number of individuals who may consume more than 1 milligram of folic acid daily with higher levels of fortification.<sup>10</sup>

### Recommendations from other groups

The U.S. Public Health Service, CDC, American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics, American Dietetic Association, and March of Dimes Birth Defects Foundation all recommend that women of childbearing age consume 400 micrograms of folic acid daily to reduce their risk for NTDs.<sup>6,32-35</sup> Additionally, the American Academy of Pediatrics, American Dietetic Association, March of Dimes Birth Defects Foundation, and CDC Working Group on Folic Acid officially support some type of folic acid fortification but do not specify a level.<sup>33-36</sup> The American Dietetic Association and American Academy of Pediatrics favor fortification of the food supply in general to protect against nutrient insufficiencies but do not officially comment on the planned level of folic acid fortification.<sup>37</sup> Some of ACOG's members believe women will fall short of the needed amount of folic acid with a fortification level of 140 micrograms and advise physicians to prescribe additional folic acid supplements.<sup>38,39</sup> Furthermore, the Birth Defects and Developmental Disabilities Division of CDC advocates fortification at the higher level of 350 micrograms per 100 grams product.<sup>40</sup>

### Rationale Statement

The benefits of a food-fortification policy are evident for several reasons. For one, there are health cost savings at all levels of a fortification program compared to no intervention. Secondly, there is strong, empirical evidence that increased folic acid consumption may also reduce the risk of cardiovascular disease and other deficiency states such as anemia. Therefore, the total savings and cost-effectiveness analyses of a fortification program have likely been underestimated because broader health benefits, such as those possible from decreased risks of coronary heart disease, have not been quantified.

The ACPM recommendation for fortification, but at a higher level of 350 micrograms, considers improved cost effectiveness, existing low average dietary folate consumption, and risk of neurologic complications from B-12 deficiency. While the highest level, 700 micrograms, may prevent the most NTDs and be the most cost-effective, this level of fortification runs the highest risk of causing harm to other population groups. A level of 140 micrograms is the least cost-effective compared to the higher alternatives and prevents substantially fewer NTDs. Based on the estimated consumption of fortified foods, the 140-microgram level may also fail to raise folic acid intakes enough to adequately protect against NTDs.

### Recommendations of the American College of Preventive Medicine

ACPM supports a fortification policy of enriched foods with folic acid to reduce the occurrence of NTDs. At this time, a level of at least 350 micrograms appears to be the most appropriate fortification level to maximize the prevention of NTDs, while protecting the health of the general population. The fortification program should be complete with surveillance measures of effectiveness and adverse outcomes. Increasing evidence regarding positive and negative effects of folate supplementation obtained from surveillance data, as well as increased scientific evidence regarding other health benefits of folate consumption, may affect ACPM's recommendation in the future.

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The Robert Wood Johnson Foundation announced its support for a national Blue Ribbon Panel charged with developing a plan to reduce sharply the number of babies born each year with spina bifida and related birth defects.

The central aim of the panel is to promote the increased intake of folic acid or folate among women in their childbearing years. Experts believe that increasing the consumption of this particular B vitamin has been proven to reduce the risk of spina bifida and related birth defects by at least 50%.

Steven H. Zeisel, MD, PhD, of the department of nutrition at UNC-CH, will serve as the scientific director for the yearlong project. National experts from the fields of pediatrics, women's health, managed health care, and birth-defects prevention have agreed to serve on the panel.

The work of the panel will complement efforts by the March of Dimes and the Centers for Disease Control and Prevention (CDC) to promote intake of folic acid or folate. For more information, contact Lisa Katz at 919-966-8498.

**American College of  
Preventive Medicine**

June 10, 1999

**LEADERSHIP  
IN THE SCIENCE,  
POLICY AND  
PRACTICE OF  
PREVENTIVE  
MEDICINE**

Jane E. Henney, MD  
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On behalf of the American College of Preventive Medicine (ACPM), I am writing to urge the FDA to update its 1996 policy requiring the fortification of food with folic acid to reduce neural tube defects in children. ACPM's review of the evidence, detailed in the April issue of *American Journal of Preventive Medicine (AJPM)* which is enclosed, finds that fortifying enriched grain products with 350 micrograms of folic acid per 100 grams of a product, would prevent 555 cases of neural tube defects each year, 466 cases more than at the 140-microgram level which is the current FDA standard.

While we understand there are reduced health costs with a fortification program compared to no program, cost-effectiveness analyses predict that a fortification program will save \$98 million in medical costs with a 350-microgram fortification program, but only \$15 million with a 140-microgram fortification program. A level of at least 350 micrograms appears to be the most appropriate fortification level to maximize the prevention of neural tube defects, while protecting the health of the general population. A fortification level of 140 micrograms is less cost effective and may also fail to raise the folic acid intake to adequately protect against neural tube defects.

The National Center for Health Statistics reports that women are not getting enough folic acid in their diets -- on average, U.S. women of childbearing age (15 - 44 years of age) consume only about half of the folate recommended. Only 66% of women report ever hearing of folic acid; only 16% report knowledge that it helps reduce birth defects; and only 9% report knowledge that it should be taken before pregnancy, according to a 1997 March of Dimes Birth Defects Foundation survey. Adequate folic acid levels are required during the first 28-30 days of gestation, prior to the closure of the neural tube. Neural tube defects such as spina bifida affect approximately 4,000 live births and pregnancies each year in the United States. Neural tube defects are associated with 1.3% of all infant deaths and are second only to

**ACPM**

cardiac defects as the leading cause of perinatal mortality from all birth defects.

ACPM is the national medical society of physicians whose primary interest and expertise are in disease prevention and health promotion. Specialists in preventive medicine are uniquely trained in both clinical medicine and public health. They have skills needed to understand and reduce the risks of disease, disability and death in individuals and in population groups. Physicians trained in preventive medicine work in public health and community agencies, in health care delivery organizations and systems, in primary care settings, in workplaces, and in academia. The College membership constitutes a major national resource of expertise in disease prevention and health promotion, areas vital to protecting and improving the nation's health.

We appreciate your attention to this issue and stand ready to assist should you require additional assistance.

Sincerely,

A handwritten signature in cursive script that reads "George K. Anderson".

George K. Anderson, MD  
President

Enclosure