**ABSTRACT**

**Introduction**

Spina bifida and anencephaly are birth defects of multifactorial etiology related to neural tube closure (neural tube defects). Anencephaly is characterized by congenital absence of the forebrain; affected children die within several weeks after birth. Spina bifida is characterized by incomplete fusion of the vertebral arches with a protruding sac that contains meninges, spinal cord, or nerve roots. Affected children have permanent neurological deficits, such as paralysis and bladder dysfunction, corresponding to the level of the malformation. As a result, they require considerable medical attention and experience disabilities that affect survival, functional status, and economic productivity.

A program that reduces the incidence of neural tube defects could therefore produce substantial societal benefits. Several observational studies and randomized trials have suggested that periconceptual folic acid supplementation lowers the risk of neural tube defects, even among women without a previously affected pregnancy. In response, the US Public Health Service recommended, in September 1992, that “all women of childbearing age ... who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected by spina bifida or other [neural tube defects].”

Three approaches to implementing this recommendation include increasing dietary folate intake by promoting consumption of fresh vegetables and legumes, fortifying staple foods, and increasing consumption of folic acid supplements. Food fortification offers several advantages over the other two approaches. Because the neural tube closes during the 4th week of gestation, folate must be provided before many women realize that they are pregnant. In the United States, more than half of all recognized pregnancies are unplanned, and 13.2 million sexually active women of childbearing age are not using effective contraception. Fortification would reach a greater proportion of this target population because it does not require behavior modification and it eliminates the costs of packaging and marketing nutritional supplements. Dietary modification would also require behavioral change, although other benefits might accrue (e.g., decreased colon cancer due to higher fiber intake). For these reasons, the US Food and Drug Administration (FDA) recently proposed amending the standards of identity for enriched grain products to include folic acid (at a level twice that necessary to replace milling losses).

Cost-benefit analysis provides a structured framework for comparing anticipated costs and benefits so that strategies likely to produce net benefits can be identified. Our recent study of the total costs attributable to 18 major birth defects in the United States may yield a substantial economic benefit. We have underestimated net benefits because of unmeasured costs of neural tube defects and unmeasured benefits of higher folate intake. We may have overestimated net benefits if the cost of neurologic sequelae related to delayed diagnosis of vitamin B12 deficiency exceeds our projection.

**Methods.** A cost–benefit analysis based on the US population, using the human capital approach to estimate the costs associated with preventable neural tube defects, was conducted.

**Results.** Under a range of assumptions about discount rates, baseline folate intake, the effectiveness of folate in preventing neural tube defects, the threshold dose that minimizes risk, and the cost of surveillance, fortification would likely yield a net economic benefit. The best estimate of this benefit is $94 million with low-level (140 micrograms [mcg] per 100 g grain) fortification and $252 million with high-level (350 mcg/100 g) fortification. The benefit-to-cost ratio is estimated at 4.3:1 for low-level and 6.1:1 for high-level fortification.

**Conclusions.** By averting costly birth defects, folic acid fortification of grain in the United States may yield a substantial economic benefit. We may have underestimated net benefits because of unmeasured costs of neural tube defects and unmeasured benefits of higher folate intake. We may have overestimated net benefits if the cost of neurologic sequelae related to delayed diagnosis of vitamin B12 deficiency exceeds our projection.
fants, including spina bifida, can be used to estimate the economic benefits of birth defect prevention programs. In the present analysis, we focused on the proposed fortification of grain with folic acid, although we considered dietary supplements as an alternative.

Methods

Analytic Framework and Level of Fortification

Cost-benefit analysis requires quantifying all anticipated benefits and costs of a proposed intervention. The economic benefit of fortification equals the product of the incremental cost associated with each neural tube defect case and the number of cases averted. Our estimate of the latter quantity is based on estimates of how many more women in the target population would consume adequate folate if fortification were instituted and how much an individual’s risk of having an affected child would be reduced. The economic cost of fortification includes costs related to food production and adverse health effects. Sensitivity analysis was used to test the impact of altering key assumptions.

All of our estimates are based on 2 fortification strategies selected from a list of 14 presented to the FDA’s Folic Acid Subcommittee in April 1993. These low and high strategies involve fortification of enriched cereal grains with folic acid at either 140 micrograms (mcg) (twice the level necessary to replace milling losses) or 350 mcg (five times the replacement level) per 100 g. The other strategies were clearly inadequate (e.g., fortification at 70 mcg/100 g) or dangerously insufficient (e.g., fortification of dairy products and grain). Cereal grains include flours made from wheat, rice, barley, triticale, buckwheat, corn, or rye; cornmeal or grits; rice; farina; and macaroni or pasta. Cereal grains are an obvious candidate for fortification because they are consumed by most women of childbearing age and are already subject to standards of identity for nutrient enrichment. These standards require millers who enrich their products to use a standard formula that generally includes thiamine, riboflavin, niacin, and iron. We chose 1991 as the index year because it was the most recent year from which grain production data were available.

Estimating Costs

Food production. Pure folic acid was available to food processors at a 1991 price of $115 per kilogram (T. Viespoli, oral communication, August 1993). To estimate the cost of fortifying each unit of grain, we applied an “overage” factor to reflect the additional folic acid that food processors would buy to compensate for losses during packaging, storage, and shipment. High stability has been documented during long-term storage of fortified breakfast cereals, cornmeal, grits, rice, and white flour. Although little folate loss occurs during routine baking and frozen storage of bread, folate recovery drops by 9% and 19%, respectively, after 90 minutes and 2 hours of baking at 230°C. On the basis of these studies and manufacturers’ estimates (H. Gordon, PhD, oral communication, July 1993), we applied a generous overage factor of 1.3.

Under these assumptions, the unit cost of folic acid fortification would be $0.0095 per 100 lb of grain at 140 mcg/100 g and $0.0237 per 100 lb of grain at 350 mcg/100 g. Total direct costs were estimated by multiplying these unit costs by “domestic food disappearance” in 1991 (US Department of Agriculture, unpublished data, July 1993), adjusted downward to exclude the unenriched portion that would not be fortified (Table 1). Domestic disappearance is a measure of human consumption; it represents the difference between total supply (domestic production plus imports and stocks on August 1, 1990) and other uses (exports, animal feed, nonfood uses, and stocks on August 1, 1991). We assumed that folic acid would not be added to grain destined for export, animal feed, or nonfood uses.

Table 1—Total Direct Costs Associated with the Universal Fortification of Cereal Grains in the United States with Two Levels of Folic Acid, in 1991 Dollars

<table>
<thead>
<tr>
<th>Cereal Grain</th>
<th>Total Domestic Disappearance, Million Hundred Ib</th>
<th>Currently Enriched, %</th>
<th>Cost: Folic Acid, $ x 10^6</th>
<th>Other Costs, $ x 10^6</th>
<th>Cost: Total, $ x 10^6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low Level</td>
<td>High Level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheat flour</td>
<td>344.855</td>
<td>90</td>
<td>2.95</td>
<td>7.37</td>
<td></td>
</tr>
<tr>
<td>Rice</td>
<td>42.3</td>
<td>90 (white)</td>
<td>0.27</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Corn flour/cornmeal</td>
<td>35.6</td>
<td>10</td>
<td>0.03</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Corn hominy/grits</td>
<td>8.6</td>
<td>1</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>433.32</td>
<td>80</td>
<td>3.26</td>
<td>8.14</td>
<td>24.68</td>
</tr>
</tbody>
</table>

Notes:

1. From the US Department of Agriculture’s Economic Research Service (J. Putnam, written communication, July 1993). Methods have been described by Putnam and Alishouse.
2. From written and oral communications in July 1993 with R. Henwood (Millers National Federation), J. Josland (Milling and Baking News), W. Goldsmith (USA Rice Council), M. Androux (CA Rice Promotion Board), D. Salonen (Lauhoff Grain Co), S. Rao (CONAGRA), and J. Otwell (Cook Flour Co). The current standard of identity for enriched cereal grains does not include folic acid.
3. Assumes an incremental unit cost of $.0095 per 100 lb of grain for low-level fortification (140 mcg folate/100 g) and $.0237 per 100 lb of grain for high-level fortification (350 mcg folate/100 g), including 30% overage to compensate for losses during packaging, storage, and shipment. These costs are adjusted downward to reflect the proportion of domestic production that is currently enriched (and would therefore be subject to the proposed standards of identity). Other annual costs include $2.5 million for analytical testing, $0.8 million for label changes (perpetual yield of a $20 million capitalized asset with a 4% discount rate), $16.4 million (low level) or $32.8 million (high level) for direct and indirect costs of neurologic sequelae among patients with undiagnosed vitamin B12 deficiency, and $5 million for surveillance of these sequelae.
4. Includes white flour, whole wheat flour, durum or semolina flour (8%), and farina.
5. Includes white rice (76%) and brown rice (24%). Note that substantial (20%–100%) nutrient loss occurs if consumers wash rice fortified by the inexpensive “powder” method, which is used in at least half of domestically enriched rice (K. Hargrove, Rice Millers Association, oral communication).
6. Other annual costs include $2.5 million for analytical testing, $0.8 million for label changes (perpetual yield of a $20 million capitalized asset with a 4% discount rate), $16.4 million (low level) or $32.8 million (high level) for direct and indirect costs of neurologic sequelae among patients with undiagnosed vitamin B12 deficiency, and $5 million for surveillance of these sequelae.
7. Includes white flour, whole wheat flour, durum or semolina flour (5%–10%), and farina.
8. Includes white rice (76%) and brown rice (24%). Note that substantial (20%–100%) nutrient loss occurs if consumers wash rice fortified by the inexpensive “powder” method, which is used in at least half of domestically enriched rice (K. Hargrove, Rice Millers Association, oral communication).
9. “Other annual costs include $2.5 million for analytical testing, $0.8 million for label changes (perpetual yield of a $20 million capitalized asset with a 4% discount rate), $16.4 million (low level) or $32.8 million (high level) for direct and indirect costs of neurologic sequelae among patients with undiagnosed vitamin B12 deficiency, and $5 million for surveillance of these sequelae.
10. Includes white flour, whole wheat flour, durum or semolina flour (8%), and farina.
11. Includes white rice (76%) and brown rice (24%). Note that substantial (20%–100%) nutrient loss occurs if consumers wash rice fortified by the inexpensive “powder” method, which is used in at least half of domestically enriched rice (K. Hargrove, Rice Millers Association, oral communication).
12. Excludes flour derived from rye, rice, barley, buckwheat, or triticale, because these grain products are not subject to a standard of identity for enrichment.

or to grains that lack standards of identity (e.g., flours made from rice, rye, buckwheat, barley, and triticale).

Folic acid fortification would not require additional equipment if it were limited to currently enriched grains. The cost of analytic testing to confirm appropriate folate levels in fortified products is unclear, because analytic testing is optional and many millers rely on their premix suppliers to perform periodic assays. Therefore, we applied the FDA’s estimate of $2.5 million annually. Changing of product labels was the only other cost anticipated by millers; this one-time cost would be $50 to $500 per package, or $20 million nationwide ($0.8 million annually, assuming perpetual yield at a 4% discount rate).

Fortification with folic acid does not affect the appearance, taste, or shelf life of cooked cornmeal, wheat bread, or wine. Any increase in retail grain prices would be so small that a significant reduction in demand would be unlikely. We therefore assumed that fortification would have no other production-related costs.

**Adverse health effects.** The adverse health effects of folic acid fortification are difficult to estimate. Folate-containing supplements administered to pregnant women have no long-term developmental, behavioral, or neurologic effects on children resulting from these pregnancies. Folic acid is very safe when administered to healthy subjects. However, there is concern about adverse health effects in special populations (e.g., persons taking anticonvulsant or antifolate medications and those with undiagnosed pernicious anemia).

Several anticonvulsants, including phenytoin and phenobarbital, affect folate metabolism. Since Chanarin et al. described an epileptic on phenobarbital whose seizures became uncontrolled with parenteral folic acid, researchers have speculated that folates may interfere with seizure control. In animal models, folates activate epileptic foci and reduce the ability of phenobarbitals to raise the seizure threshold, especially when applied directly to the cerebral cortex. Folic acid supplements also lower serum phenytoin levels in epileptics.

However, numerous controlled trials have found no effect of oral folic acid on seizure control at doses up to 20 mg daily.

Other commonly used medications with antifolate effects include methotrexate, pyrimethamine, trimethoprim, trimethoprim, and sulfasalazine. Folic acid (1 mg/day) does not reduce the therapeutic effectiveness of methotrexate in rheumatoid arthritis, although it may lower toxicity. Adverse drug interactions involving dietary folate are conceivable but could be avoided at minimal expense through educational efforts such as drug labels, package inserts, and professional publications. We therefore assumed that the cost of folic acid fortification related to drug interactions would be negligible.

Folates may affect the absorption or metabolism of trace minerals, especially zinc. Animal studies suggest that zinc uptake is impaired in the presence of folic acid, but a high-folate diet does not lower tissue zinc levels. Folate-containing supplements reduce zinc absorption in pregnant women and increase fecal zinc losses in healthy men, but decreased urinary excretion may compensate. A placebo-controlled trial of oral folic acid showed no effect on plasma and erythrocyte zinc levels. On the basis of these studies, we assumed that folic acid fortification would have little effect on zinc homeostasis.

The most worrisome effect of folic acid is its ability to induce remission of megaloblastic anemia due to vitamin B12 deficiency while neurologic manifestations progress. Daily doses of 300 to 500 mcg may induce partial remission, but doses of at least 1 mg are generally required for complete remission and relapses are frequent. Since 1947, at least 80 patients with vitamin B12 deficiency have developed subacute degeneration of the spinal cord or other neurologic sequelae despite hematologic improvement on folic acid. With a few exceptions, these cases involved daily folic acid intakes of 5 mg or more.Prompt administration of vitamin B12 improved neurologic symptoms in most but not all patients. A survey of 1200 hematologists in 1971 revealed that only 20 of the 860 respondents had cared for a patient during the previous decade whose neurologic illness was “made worse by the daily ingestion of 400 mcg or less of folic acid.” Only three of the seven adequately described cases met diagnostic criteria.

On the basis of limited data available in the medical and economic literature, we estimated the number of additional cases of neurologic disease likely to result from folate fortification, as well as the associated costs. Two population-based European studies reported the annual incidence of diagnosed pernicious anemia (without fortification) as 9.5 and 16.7 per 100,000 persons. The higher estimate, which included both unequivocal and possible cases, corresponds to 38,000 new cases in the United States (in 1991). With low-level or high-level fortification, about 5% or 10% (respectively) of these patients would have received enough folate to mask the anemia that led to their diagnosis (assuming a threshold of 0.85 mg/day). Our literature review corroborated an earlier finding that 24% to 26% of patients with pernicious anemia whose anemias respond to folic acid develop neurologic signs. Therefore, folate fortification in 1991 would have allowed about 500 patients with pernicious anemia to develop neurologic disease.

We then posited that all of these neurologic sequelae would have been as costly as subacute combined degeneration of the spinal cord and that every case would have required one hospitalization in 1991. According to the 1989 National Hospital Discharge Survey, the mean duration of hospitalization for patients with subacute combined degeneration or related disorders (International Classification of Diseases, 9th edition, Clinical Modification codes 336.0 to 336.8) was 16 days, and the mean cost per day (inflated to 1991 dollars) was $867. We applied a hospital to physician services cost ratio (specific to spinal cord diseases) of 4.7:1 and a multiplier of 1.83 (specific to elderly persons with neurologic disorders) to reflect the additional cost of drugs, nursing home care, appliances, and other professional services. Indirect costs were approximately 6.6% of direct costs among elderly persons with neurologic disorders, so the total economic cost of fortification-related neurologic disease was estimated at $16.4 million ($33,000 per case).

This estimate may be too high because (1) many neurologic sequelae would actually be less severe than subacute combined degeneration; (2) mild subacute combined degeneration does not require hospitalization; (3) the diagnosis and treatment of subacute combined degeneration may be delayed more than a year, so the costs may actually be paid with future (discounted) dollars; and (4) the widespread practice of assaying vitamin B12 levels in neuropathic patients would detect most cases of masked pernicious anemia at a reversible stage. However, our estimate may be too low if severe subacute combined degeneration leads to late complications or lifelong skilled nursing care. Folate fortification...
would not affect the underlying prevalence of vitamin B₁₂ deficiency, so the cost of diagnostic testing would change little.

In light of the controversy surrounding the potential impact of folic acid fortification on the incidence of subacute combined degeneration, such a program could not be implemented without follow-up surveillance. No state or federal agency collects information on the neurologic sequelae of vitamin B₁₂ deficiency. The incremental cost of this effort was estimated at $5 million (range of $1 million to $10 million; J.D. Erickson, DDS, PhD, oral communication, August 1993).

Estimating Benefits

Reduction in the risk of neural tube defects. The literature on periconceptional folate and neural tube defects includes two randomized, controlled, double-blind trials¹² and three nonrandomized trials (from one investigator) among women with a previous neural tube defect pregnancy⁶³-⁶⁵; one randomized controlled trial⁶ and one nonrandomized trial among women without such a history;⁶ six case-control studies based on maternal recall of diet or supplement use;⁶⁶-⁶⁹; and one cohort study.⁷ All but one⁶⁸ of these studies suggested a favorable effect of either dietary or supplemental folate. Supportive evidence comes from studies showing that women with a history of multiple neural tube defect pregnancies⁶⁹ and women who are carrying an affected child⁷⁰ have lower erythrocyte folate levels than matched controls. The consistency of these findings is striking, despite differences in study methods and potential confounders.⁷¹

The effectiveness of folic acid fortification is difficult to estimate from this literature. None of the three randomized trials used dietary fortification, yet the bioavailability of folic acid added to foodstuffs is 50% to 60% of that of folic acid in liquid⁶⁰ or tablet⁶⁶ form. Bioavailability may be lower in the presence of alcohol,⁷⁷ in alkaline solutions,⁷⁸ or when folic acid is added to bread⁷⁹ or foods that contain folate conjugase inhibitors.⁸⁰ All three trials were performed in high-prevalence areas, so the results may not apply to American women. However, all but one of four US studies⁶⁶-⁶⁸ and all four studies that explored the neural tube defect/diet association⁶⁷,⁸⁸,⁹⁰ are consistent with the Medical Research Council's finding of 67% effectiveness.¹ We used the Centers for Disease Control and Prevention's (CDC) estimate of 50% effectiveness, with literature-based sensitivity limits of 67%¹ and 20%.⁸⁸

The daily intake of dietary folate necessary to achieve this benefit may be as low as 100 mcg; however, two case-control studies show a graded dose-response relationship up to 311⁸⁷ or 350 mcg⁹⁰ daily. Observational studies lack the statistical power necessary to assess the effect of higher intakes. We conservatively assumed a target level of 400 mcg, which equals the proposed recommended daily allowance for pregnant or lactating women.¹⁰¹ A target level of 200 mcg was tested in a sensitivity analysis.¹⁰²,¹⁰³

Baseline folate intake. Folic acid is currently added to a limited number of foods in the United States, such as breakfast cereals, instant breakfast drinks, and other diet supplements.⁸⁸-⁹⁰ Despite voluntary efforts,¹⁰² only 8% of adult women obtained at least 400 mcg of dietary folate daily from 1976 through 1980.⁹⁴ The 1988–91 National Health and Nutrition Examination Survey found a slight improvement in the median daily folate intake of women aged 19 through 34 years, from 165 mcg to about 186 mcg in whites and from 146 mcg to about 150 mcg in blacks.¹⁰⁷ The proportion of women receiving at least 400 mcg daily from 1988 through 1991 period has not yet been reported, but it will probably remain close to 8%. This assumption is supported by data from the 1985–1986 Continuing Survey of Food Intake by Individuals.¹⁰⁸

In the 1986 National Health Interview Survey, 27% of nonpregnant women 18 to 44 years of age had used a folate-containing supplement at least once during the preceding 2 weeks.¹⁰⁹ About 71% of these supplements were taken daily; most provided at least 100% of the 1986 recommended daily allowance (RDA) for nonpregnant, nonlactating women (400 mcg). Several population-based studies conducted in the 1980s confirm these estimates, with regular supplement use rates of 12% to 15% during the periconceptional period.⁸⁶-⁸⁸ In two of these studies, ⁷%⁸⁸ and ⁹%⁸⁷ of the control women received partial supplementation.

Our best estimate of the percentage of women in the target population already receiving enough folate to minimize the risk of a neural tube defect is 33% (27% from supplements, 8% from diet, 2% from both). For sensitivity analysis, this percentage could be as low as 13% or as high as 40% if supplement use has increased since 1987. If the threshold for lowering the risk of neural tube defects is actually 200 mcg instead of 400 mcg, then 56% of the target population is receiving adequate folate (27% from supplements, 40% from diet, 11% from both).

Effect of fortification on folate intake. According to the FDA's analysis of data from the 1987/88 Nationwide Food Consumption Survey, grain fortification at 140 mcg per 100 g would enable about 50% of women 11 to 50 years of age to receive at least 400 mcg of folate daily from all sources.¹² Grain fortification at 350 mcg per 100 g would enable about 75% of women in this age group to receive the desired amount of folate. The portions of the target population that would begin consuming adequate folate after fortification would be 17% (50% – 33%) with low-level fortification and 42% (75% – 33%) with high-level fortification. Although actual food intake is 18% to 30% higher than that reported in consumption surveys,¹¹,¹² about 20% of the domestic cereal grain produced is unenriched (Table 1). These effects roughly cancel each other. If the threshold for lowering the risk of neural tube defects is actually 200 mcg instead of 400 mcg, then the portions of the target population likely to benefit are 29% (85% – 56%) with low-level fortification and 39% (95% – 56%) with high-level fortification.

Value of preventing a neural tube defect. The benefit of preventing each neural tube defect case equals the net present value of total lifetime costs associated with a child in the 1991 birth cohort after subtracting the costs associated with an average child.¹¹ We assumed that, if a neural tube defect case had been prevented by adequate folate intake, the affected child would have been born with the baseline risk of other defects or illnesses. Because the unit of analysis was the individual, our estimates for spina bifida include the costs of associated anomalies and illnesses. Our best estimate incorporates a discount rate of 4%, although we tested rates of 2.5% and 6.0% in sensitivity analyses.

For spina bifida, the total cost represents the sum of five components of direct cost: (1) acute inpatient services, estimated with the California Patient Discharge Data Set, the MediCal claims file, and budget data from Shriner's Hospitals; (2) outpatient health services, estimated with the MediCal claims file; (3) long-term care services, estimated with the MediCal claims file and the California Department of Developmental Services masterfile; (4) developmental services...
outside the state’s seven inpatient centers, estimated with the just-mentioned master-file; and (5) special education services, estimated with the 1985 through 1989 National Health Interview Surveys, the National Longitudinal Transition Study of Special Education Students, and California special education enrollment and expenditure data. Two components of indirect cost were also used: (1) mortality, estimated with survival data from published cohorts, earnings data from the US Bureau of the Census, and labor market participation rates from the US Department of Labor; and (2) morbidity, estimated with these data sources, the National Health Interview Survey, and the Survey of Income and Program Participation. Indirect cost estimates were based on the human capital approach. The 1987 National Medical Expenditure Survey was used to calculate incremental medical costs relative to an average child.

For anencephaly, incremental direct costs were assumed to be zero. Anencephaly is rapidly and uniformly fatal, so there are no outpatient, long-term care, developmental, or special education costs. There are also no morbidity costs; all anencephalic births incur the costs associated with premature mortality. In accord with the cost of illness methodology, consumption savings attributable to early mortality were not considered.

Table 2 shows our final estimates of per capita costs for the average American child born with spina bifida in 1991. Our original estimates were based on California data from 1988; we deflated these estimates by the California to US ratio of average annual earnings and inflated the resulting totals to 1991 dollars using the medical care component of the consumer price index (for medical costs) or the civilian employment cost index (for nonmedical costs). The aggregate cost in 1991 dollars, with 4% discounting, was $349 133 per child. These figures are comparable to the CDC’s rough estimate of $250 000 per child. Other estimates are incomplete or inapplicable to the United States.12,13

The estimated per capita cost of an anencephalic child born in 1991 (Table 2) equals the net present value of all future earnings (with an imputed value for household production) over the entire period of labor force participation. At a discount rate of 4%, this quantity was estimated at $485 016 per child. In accord with standard methods,17-113 we did not attribute costs to aborted or stillborn fetuses.

Other effects of fortification. Folates may improve perinatal outcomes independent of their effect on neural tube closure. In indigent populations, high serum folate levels are related to more favorable birthweight distributions.114 and folic acid supplements raise mean birthweight.115,116

In well-nourished populations, observational117,118 and randomized studies119-122 have produced inconsistent results. Chemical evidence of folate deficiency is common among high-risk pregnant women,123,124 but its significance is unclear. Tolorova reported that multivitamins with folic acid may prevent recurrences of facial clefts.125 This conclusion was consistent with those of previous nonrandomized studies126,127 but was refuted by two randomized controlled trials.3,128 Given conflicting evidence, we assumed that folic acid fortification would not affect the incidence of low birthweight and cleft deformities. Although animal studies suggest that folates may reduce the teratogenicity of valproic acid,129,130 the applicability of this finding to humans is unknown.

Folate deficiency may be a factor in carcinogenesis.131 Although a preliminary study of women with mild to moderate cervical dysplasia suggested that 3 months of folic acid supplementation may induce regression of cytologic abnormalities,132 this result was not confirmed in a larger study of 6 months’ duration.133 Furthermore, invasive cervical cancer is not associated with dietary folate intake.134-136 Patients with ulcerative colitis may lower their risk of colorectal cancer by consuming supplemental folate acid.137 Folic acid with vitamin B₁₂ may decrease host susceptibility to carcinogens,138 but it is unclear whether fortification of grain would affect the incidence of cancer.

Finally, low plasma folate levels and folate-deficient diets have been linked to high homocysteine levels,139 which in turn are associated with increased risk of atherosclerosis.140 Although folate supplementation may reverse hyperhomocysteinemia,141 its effect on atherosclerosis remains speculative.

Results

Best Estimate of Net Benefit

According to combined data from 16 state-based birth defects surveillance systems, the prevalence of spina bifida between 1983 and 1990 was 4.6 per 10 000 live births.142 A similar estimate of 4.4 per 10 000 live births was derived from the CDC’s Birth Defects Monitoring Program. The birth prevalence of anencephaly was more difficult to ascertain because these infants are considered stillborn in some areas. The California Birth Defects Monitoring Program has reported that anencephaly occurs in 2.7 per 10 000 live births (T. Bateson, written communication, July 1993).

Assuming that adequate folic acid intake lowers the risk of a neural tube defect pregnancy by 50%, the target population can be separated into two subpopulations. Among the 33% who receive adequate folate (≥ 400 mcg/day), the expected prevalences of spina bifida and anencephaly would be 2.7 and 1.6 per 10 000 live births, respectively. Among the 67% who receive inadequate folic acid, the expected prevalences of spina bifida and anencephaly would be twice as high, or 5.5 and 3.2 per 10 000 live births. Low-level fortification of grain would shift 17% of the target population from high risk to low risk, whereas high-level fortification would

| TABLE 2—Total Incremental Costs ($) Associated with One Case of Spina Bifida or Anencephaly, by Discount Rate: United States, 1991 |
|-----------------|------------------|------------------|------------------|
| Spina bifida | | |
| Medical care | 121 279 | 140 411 |
| Developmental services | 1 481 | 1 541 |
| Special education | 29 349 | 30 546 |
| Indirect: mortality cost | 201 991 | 210 232 |
| Indirect: morbidity cost | 127 354 | 132 550 |
| Total costs | 481 454 | 515 280 |
| Anencephaly | | |
| Indirect: mortality cost | 808 043 | 841 009 |
| Total costs | 808 043 | 841 009 |

Folic Acid Fortification

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TABLE 3—Sensitivity Analysis of the Net Economic Benefit and the Benefit–Cost Ratio Associated with Low-Level and High-Level Folic Acid Fortification of Cereal Grains, United States, 1991

<table>
<thead>
<tr>
<th>Assumption and Value Assigned</th>
<th>Net Economic Benefit, $ \times 10^8</th>
<th>Ratio of Benefits to Costs</th>
<th>Cost per Case Averted, $ \times 10^3</th>
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<tbody>
<tr>
<td></td>
<td>Low Level</td>
<td>High Level</td>
<td>Low Level</td>
</tr>
<tr>
<td>Discount rate, %</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2.5</td>
<td>165.1</td>
<td>429.6</td>
<td>6.8</td>
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<tr>
<td>4.0 (best estimate)</td>
<td>93.6</td>
<td>251.7</td>
<td>4.3</td>
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<td>6.0</td>
<td>44.5</td>
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<td>Members of target population</td>
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<tr>
<td>intake at baseline, %</td>
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<td>13</td>
<td>208.6</td>
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</tr>
<tr>
<td>33 (best estimate)</td>
<td>93.6</td>
<td>251.7</td>
<td>4.3</td>
</tr>
<tr>
<td>40</td>
<td>46.7</td>
<td>212.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Reduction in risk of neural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tube defect associated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with adequate folate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intake, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>15.2</td>
<td>58.3</td>
<td>1.5</td>
</tr>
<tr>
<td>50 (best estimate)</td>
<td>93.6</td>
<td>251.7</td>
<td>4.3</td>
</tr>
<tr>
<td>67</td>
<td>146.6</td>
<td>382.7</td>
<td>6.2</td>
</tr>
<tr>
<td>Folate intake necessary to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>minimize risk of neural tube</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>defect thresholds (threshold</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dose), mcg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>213.0</td>
<td>274.5</td>
<td>8.6</td>
</tr>
<tr>
<td>400 (best estimate)</td>
<td>93.6</td>
<td>251.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Cost of surveillance program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1 million</td>
<td>97.6</td>
<td>255.7</td>
<td>5.1</td>
</tr>
<tr>
<td>$5 million (best estimate)</td>
<td>93.6</td>
<td>251.7</td>
<td>4.3</td>
</tr>
<tr>
<td>$10 million</td>
<td>88.6</td>
<td>246.7</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Note. The best estimate is based on the following assumptions: (1) the discount rate is 4.0%; (2) 33% of the target population has adequate folate intake at baseline (from diet or vitamin supplements); (3) adequate folate intake reduces the risk of a neural tube defect pregnancy by 50%; (4) a threshold daily dose of folate necessary to minimize the risk of a neural tube defect pregnancy is 400 mcg; and (5) the cost of a surveillance program to monitor adverse effects is $5 million.

The net economic benefit represents the difference between total benefit and total cost, where:

\[ \text{Total Cost} = \text{Cost}_{\text{total}} + \text{Cost}_{\text{spending}} + \text{Cost}_{\text{tests}} + \text{Cost}_{\text{surveillance}} + \text{Cost}_{\text{store. d. collagen}} \]

\[ \text{Total Benefit} = \sum (L_{B_{(d)})} \times (A_{D_{(P_{(d)}} - A_{D_{(V_{(d)}}}) \times (NT_{D_{(P_{(d)}}} - NT_{D_{(V_{(d)}}}) \times \text{PERCAP}) \]

*L1_{B_{(d)}} is the number of live births in the United States in 1991; A_{D_{(P_{(d)}}} and A_{D_{(V_{(d)}}} are the proportions of the target population receiving enough folate to minimize the risk of a neural tube defect after and before fortification, NT_{D_{(P_{(d)}}} and NT_{D_{(V_{(d)}}} are hypothetical neural tube defect incidence rates without and with adequate folate intake, and PERCAP is the lifetime total of direct and indirect costs associated with one infant born with a neural tube defect in 1991. This quantity is summed across neural tube defects (e.g., spina bifida plus anencephaly).

*The net economic benefit is based on the following assumptions: (1) the discount rate is 4.0%; (2) 33% of the target population has adequate folate intake at baseline (from diet or vitamin supplements); (3) adequate folate intake reduces the risk of a neural tube defect pregnancy by 50%; (4) a threshold daily dose of folate necessary to minimize the risk of a neural tube defect pregnancy is 400 mcg; and (5) the cost of a surveillance program to monitor adverse effects is $5 million.

The economic benefits from preventing these neural tube defects amount to $121.5 million with low-level fortification and $300.9 million with high-level fortification. These figures far exceed the costs of fortification shown in the last column of Table 1; the differences of $93.6 million (low level) and $251.7 million (high level) represent the net benefit of fortification. The estimated benefit–cost ratios are 4.3:1 for low-level fortification and 6.1:1 for high-level fortification.

**Sensitivity Analysis**

Table 3 shows the net economic benefit and the benefit–cost ratio computed under a range of assumptions about the discount rate, the baseline level of fortification shown in the target population, the effectiveness of dietary folate in preventing neural tube defects, the threshold dose of folic acid; that minimizes the risk of an affected child, and the cost of comprehensive surveillance. The benefit–cost ratio remains favorable with any plausible value of these variables.

**Cost-Effectiveness Compared with Supplement Use**

Promoting voluntary use of folate supplements is another strategy to prevent neural tube defects. We could not estimate the net economic benefit of such a program, because adherence is not predictable. The cost per neural tube defect averted, a measure of cost-effectiveness, was estimated, assuming that (1) all folate supplements have at least 400 mcg of folic acid, (2) all purchased supplements would be consumed, (3) only members of the target population would respond to a public education campaign, (4) no members of this population would develop neurologic sequelae of vitamin B12 deficiency, (5) excess consumption beyond 400 mcg daily would be negligible, and (6) supplement use would be independent of dietary folate intake. At a minimum annualized price of $12 ($3.29/100 tablets; Davis CA), US consumers would spend $132,000 to avert each neural tube defect case. The comparable cost per neural tube defect averted would be $92,000 for low-level fortification and $65,000 for high-level fortification (Table 3).

**Discussion**

This analysis shows that fortification of cereal grains in the United States with folic acid would probably have economic benefits that significantly exceed the costs under a wide range of assumptions. Although high-level fortification might have greater net economic benefits and a larger cost–benefit ratio than low-level fortification, the latter strategy may be preferable in the short term because it poses little risk to persons with undiagnosed vitamin B12 deficiency. With low-level fortification, only 5% of adults more than 50 years of age would consume 850 mcg or more of folate daily. If future surveillance reveals no adverse consequences, the fortification level could be increased to reach a greater proportion of the target population.

The economic benefit of averting a neural tube defect may be significantly shift 42% of the target population. There were 4,111,000 live births in the United States in 1991; thus, low-level fortification would have averted 1,911 spina bifida cases and 1,131 anencephaly cases, and high-level fortification would have averted 473 spina bifida cases and 280 anencephaly cases.

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greater than we estimated because several categories of costs could not be assessed. For example, parents have out-of-pocket expenses related to nonprescription medications, home modification, special transportation, and supplies. Among 112 families of children with spina bifida, median out-of-pocket expenses were $2583 in 1984. To the extent that children with spina bifida require more attention than normal children, their parents incur opportunity costs that are difficult to quantify. Mothers of children with spina bifida are less likely than matched controls to work outside the home; parents may enjoy a lower standard of living. In comparison with control parents, fathers of affected children report more psychological and somatic health problems, mothers are more likely to feel depressed or run down, parental fertility is reduced, and divorce occurs more often.

Although the human capital approach is widely applied in cost–benefit analysis, it has limitations. Because the indirect costs of illness are based on the market value of production, this approach undervalues people with low market productivity (e.g., elderly people, women, and minorities) and ignores the psychosocial costs of disease. The willingness-to-pay approach, a theoretically preferable alternative, is based on how much one would be willing to pay for a specific risk reduction. However, this approach also has limitations in the face of externalities and other forms of “market failure.” Aggregating individual valuations to assess societal benefits is problematic, and the maldistribution of wealth can lead to undervaluations similar to those noted with the human capital approach. Eliciting what individuals are willing to pay in the face of complex hypothetical outcomes involves reliance on interview and surrogate market techniques that generate widely varying estimates. Willingness-to-pay valuations tend to be an order of magnitude higher than human capital approaches.


Food and Drug Administration. Options document. Presented at the Folic Acid Subcommittee meeting; April 15, 1993.

Crystal City, Va.


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