



Reevaluating the Benefits of Folic Acid Fortification in the United States: Economic Analysis, Regulation, and Public Health

Scott D. Grosse, PhD, Norman J. Waitzman, PhD, Patrick S. Romano, MD, MPH, and Joseph Mulinare, MD, MPH

Before a 1996 US regulation requiring fortification of enriched cereal-grain products with folic acid, 3 economic evaluations projected net economic benefits or cost savings of folic acid fortification resulting from the prevention of pregnancies affected by a neural tube defect. Because the observed decline in neural tube defect rates is greater than was forecast before fortification, the economic gains are correspondingly larger.

Applying both cost-benefit and cost-effectiveness analytic techniques, we estimated that folic acid fortification is associated with annual economic benefit of \$312 million to \$425 million. The cost savings (net reduction in direct costs) were estimated to be in the range of \$88 million to \$145 million per year. (*Am J Public Health*. 2005; 95:1917–1922. doi:10.2105/AJPH.2004.058859)

ON MARCH 5, 1996, THE US

Food and Drug Administration (FDA) required that manufacturers fortify enriched cereal-grain products with 140 µg of folic acid per 100 g of cereal-grain product by January 1, 1998.¹ This decision was intended to ensure that women who become

pregnant would be provided access to a nutrient that can prevent a substantial proportion of neural tube defects (NTDs).²

Before the adoption of fortification in 1996, 3 studies projected net economic benefits from fortification.^{3–5} To date, no analysis has evaluated the costs and benefits realized by fortification. We calculated the economic impact of fortification using both cost-benefit and cost-effectiveness analytic techniques on the basis of prefortification and postfortification epidemiological data. We also discuss how observed changes in NTD rates differ from those forecast before fortification and the implication for modeling on the basis of incomplete data.

Economic Evaluation and the Policy Process

Economic evaluation plays an important role in translating research findings into practice and policy. Economic evaluations can be “ex ante,” conducted before the adoption of a policy on the basis of results from pilot studies and theoretical assumptions, or “ex post,” carried out after implementation using information on observed outcomes. Ex ante analyses are not often compared with ex post analyses on the basis of documented results of

policies. This is unfortunate, because policies may have unanticipated consequences.

Since the Reagan administration, the executive branch has required regulatory agencies to conduct a regulatory impact analysis of proposed rules. Under Executive Order 12866 signed in 1993, “significant regulatory actions” are to be accompanied by an assessment of expected costs and benefits.⁶ No requirement exists that new or revised regulatory impact analyses be prepared after the implementation of regulations to validate the projected benefits and costs on the basis of observed impacts.

Two types of economic evaluation are used to inform public health decisions. One is cost-benefit analysis (CBA). A CBA values all outcomes in monetary terms, including deaths and cases of disease averted. The other type is cost-effectiveness analysis (CEA). A CEA calculates the ratio of net costs (intervention costs minus medical and other direct costs averted from prevention) to the numbers of health outcomes.⁷ Health outcomes can be expressed in natural units (e.g., deaths averted) or with a measure that integrates mortality and morbidity, such as quality-

adjusted life years. Guidelines recommend use of the quality-adjusted life year as a common metric to enhance the comparability of CEAs.⁸

Until recently, regulatory analyses have mostly taken the form of CBAs. In contrast, most medical or public health evaluations have been CEAs. In September 2003, the Office of Management and Budget (OMB) directed agencies to begin using both CEA and CBA “for all major rulemakings for which the primary benefits are improved public health and safety.”^{9,10}

Economic evaluations are not necessarily used to determine regulatory decisions. Each federal agency is governed by specific legislation. In particular, the Food, Drug, and Cosmetic Act requires FDA to base decisions on safety and efficacy.¹¹ For food additives, FDA follows a safety standard of a reasonable certainty of no harm and does not directly take into account projected economic benefit. Cost-effectiveness calculations can still indirectly influence regulatory decisions.¹²

Folic Acid and Health Outcomes

Between 1981 and 1992, several studies reported that



consumption of vitamin supplements containing folic acid before conception was associated with a reduction of 50% to 75% of cases of spina bifida and anencephaly.¹³⁻¹⁷ More conclusively, a multicenter randomized trial in 1991 demonstrated that folic acid protects against recurrence of NTD-affected pregnancies.¹⁸ A randomized-controlled trial in Hungary in 1992 found that multivitamins containing folic acid have a protective effect on NTDs in women without a previously affected pregnancy.¹⁹

On the basis of this evidence, the US Public Health Service issued a recommendation in September 1992 that all women capable of having children consume 400 µg per day of folic acid to reduce the numbers of pregnancies affected by spina bifida and other NTDs.²⁰ Although folic acid can be obtained through vitamin supplements, women with unplanned pregnancies, accounting for up to 50% of all live births in the United States, are much less likely to consume vitamin supplements before conception.²¹ The simplest approach to ensuring that women are protected before the onset of pregnancy is to routinely add folic acid to commonly consumed foods.

Any intervention needs to be evaluated for risks of harm. The major concern with adding folic acid to foods is that individuals with undiagnosed vitamin B₁₂ deficiency could experience a delay in receiving a diagnosis. The fear is that high intakes of folic acid could “mask” the hematologic manifestation of anemia

while allowing neurological damage to proceed untreated.² The evidence for the masking hypothesis is circumstantial.²² Folic acid shares a metabolic pathway with vitamin B₁₂, and the anemia associated with vitamin B₁₂ deficiency can be resolved by increasing the intake of folic acid. Prolonged deficiency of vitamin B₁₂ can result in neurological damage, which, if left untreated, can be disabling and irreversible. Case reports in the 1940s and 1950s documented that certain individuals with pernicious anemia who were taken off therapy with liver extracts rich in vitamin B₁₂ and, instead, received high-dose folic acid supplements (generally 5 mg/day or greater) experienced progressive neurological damage without anemia.²³

The level of folic acid intake above which individuals with undiagnosed vitamin B₁₂ deficiency are at risk of delayed diagnosis and neurological progression is uncertain. FDA set a safe upper level of consumption of 1 mg/day of total folate, not distinguishing synthetic folic acid from natural folate.^{24,25} The Institute of Medicine (IOM), in 1998, also set a tolerable upper

intake level (UL) of 1 mg/day, but made this specific to folic acid and excluded natural folate. The IOM reported that the lowest observed adverse effect level (LOAEL) is 5 mg/day, meaning that there is little evidence of harm for intakes below that level, but used an uncertainty factor of 5 below the LOAEL to set the UL.²³

Ex Ante Economic Evaluations of Folic Acid Fortification

Three economic evaluations were prepared before the 1996 decision to require folic acid fortification of enriched cereal-grain products. A CBA was prepared by FDA staff and published in 1993.³ A second CBA was published in 1995 by University of California researchers.^{4,26} A third CEA was published in 1996 by CDC researchers.⁵ The findings of both the California and CDC analyses were presented to the FDA Folic Acid Subcommittee before CBA publication and before the fortification mandate was issued.

Table 1 summarizes the results of the 3 ex ante economic studies for the level of 140 µg of folic acid per 100 g of cereal-grain

product. The estimate of net monetary benefit in the 2 CBA studies was roughly \$700 million in the FDA analysis and \$100 million in the California analysis. The CDC analysis did not calculate net monetary benefit but did estimate \$5 million in direct cost savings.

The FDA and California estimates of net benefit diverged because of differences between the willingness-to-pay (WTP) method used in the FDA analysis and the cost-of-illness (COI) method used in the California study. The FDA approach valued deaths averted at \$5 million, on the basis of the calculated risk premium for fatal on-the-job injuries.³ The California approach valued deaths according to lost productivity in future years discounted to present value at a 5% discount rate, which, in 1991, was \$342 500 at birth.²⁶

The 3 studies used similar fortification cost estimates. The annual cost of fortificant was assumed to be \$4 million in the FDA and CDC analyses and \$3.3 million in the California analysis. All 3 analyses assumed \$2.5 million in analytic testing by manufacturers. In the FDA analysis, the cost of changing food labels

TABLE 1—Summary of Ex Ante Economic Evaluations of Folic Acid Fortification at 140 µg/100 g

Study (Currency y)	No. of NTDs Averted (% Reduction)	No. of Cases Neurological Damage	Benefit from NTD Prevention, \$ Millions	Fortification Costs, \$ Millions	Adverse Health Effects Costs (\$)	Net Benefit, \$ Millions
FDA (not stated)	116 (4.6%)	0	651-786	27	NA	624-759
California (1991)	304 (10.5%)	500	121.5	11.5	16.4m	93.6
CDC (1993)	89 (2.3%)	89	16.1	11	350 000	4.7

Note. NTD = neural tube defects, or cases of spina bifida and anencephaly; m = millions.



was a 1-time cost of \$20 million, which was converted to an annualized cost of \$800 000 per year in perpetuity in the California analysis and \$4.5 million in annualized cost in the CDC study. The California study assumed that surveillance of adverse effects would be funded at \$5 million per year.

The analyses differed with regard to the expected costs of adverse effects. The FDA assumed no adverse effects with fortification at 140 μg of folic acid per 100 g of cereal-grain product. Projections of costs of adverse health effects were higher in the California study (\$16.4 million) than in the CDC study (\$350 000). The 2 studies differed in the numbers of cases of adverse effects, 500 and 89, respectively, and the average cost per case of neurological damage, \$33 500 and \$3900, respectively.

Fortification and NTD rates

All 3 ex ante analyses projected modest percentage reductions in NTD rates from fortification at 140 μg of folic acid per 100 g of cereal-grain product, from 2 to 10% (Table 1). After implementation of folic acid fortification in the United States, analyses of birth defects surveillance data have estimated substantially larger reductions in NTD, between 20 and 30%. Data on births with spina bifida and anencephaly from programs without prenatal diagnosis indicate a reduction of 23% between 1995–1996 and 1998–1999, and programs that included information on prenatally ascer-

tained cases recorded a 30% reduction in NTDs.²⁷

Why the difference between the projected outcomes and the observed reductions? First, rather than an increase in intake of 100 $\mu\text{g}/\text{day}$ as projected, the average increase in intake in the US adult population may be closer to 200 $\mu\text{g}/\text{day}$, estimated on the basis of observed changes in serum folate levels.²⁸ Analysis of folate in enriched foods reveals that certain foods contain more than the expected amount, with enriched bakery products reported to contain 40% to 100% more folic acid than stated.²⁹ Vitamin supplements and breakfast cereals that are enriched with 400 μg of folic acid per serving may have also contributed, although the contribution of supplements is small. Surveys conducted by the March of Dimes indicate only a small increase during this period in consumption of supplements containing folic acid by women of childbearing age, rising from 28% in 1995 to 32% in 1998 and remaining at that level through 2003.^{30,31}

Second, the ex ante economic analyses were very conservative in modeling of the folate-NTD association because of a lack of information on a dose–response group curve. All 3 analyses assumed that only women consuming 400 $\mu\text{g}/\text{day}$ or more would have a reduced risk of having a NTD-affected pregnancy. Data from Ireland subsequently showed a dose–response group relation between blood folate levels and decreased NTD risk.³² On the basis of those data and other assumptions, a

100 $\mu\text{g}/\text{day}$ increase in folic acid consumption would be expected to lead to a reduction in NTD rates in the United States of 13%²⁸ to 22%,³³ whereas a 200 $\mu\text{g}/\text{day}$ increase would be associated with a 23%²⁸ to 41%³³ reduction.

The California study treated natural folate and synthetic folic acid as equivalent, whereas the CDC study assumed that only synthetic folic acid would provide protection against the risk of NTDs. It has long been known that naturally occurring food folate is limited in bioavailability compared with synthetic folic acid. The IOM recently concluded that the bioavailability of folic acid in food is 1.7 times greater than that of natural folate.²³ Thus, folate has some protective effect against NTDs but less than that of folic acid.

Canadian authorities also mandated folic acid fortification in 1998, at 150 $\mu\text{g}/100$ g of flour. The reported percentage reductions in NTDs (spina bifida and/or anencephaly) in provinces in the eastern half of Canada range from 32% to 78%.^{34–38} The greater percentage declines in these provinces compared with the United States reflect higher baseline NTD rates; the postfortification NTD rate in each province was approximately 1 per 1000. Similarly, folic acid supplementation in China resulted in a greater decline in areas with higher NTD baseline rates.³⁹

Ex Post Economic Evaluation of Fortification

We performed a preliminary ex post economic evaluation of

folic acid fortification in the United States. The only health benefit considered was the prevention of NTD births. Published evidence suggests that multivitamins containing folic acid may be protective against other types of birth defects as well.⁴⁰ In addition, the reported associations between folic acid intakes and homocysteine levels and between homocysteine levels and cardiovascular disease suggest possible decreases in cardiovascular outcomes such as stroke.²² Upon the publication of conclusive data on other health end points influenced by fortification, these could be incorporated in a comprehensive economic evaluation.

METHODS

In line with the OMB guidance recommending that both CEA and CBA be used to evaluate regulatory actions affecting public health, we present preliminary estimates of the economic impact of folic acid fortification in both forms. For the CBA, we used the same COI method used in the California CBA study. WTP estimates for the prevention of congenital anomalies require additional development. In addition, we calculated the reduction in averted direct costs, which can be directly compared with the CDC ex ante CEA study.

We excluded NTD-affected pregnancies not ending in live birth because of the relatively low direct costs and difficulties with the attribution of indirect costs, as well as the issue of costs associated with replacement births.



Birth defects surveillance data indicate reductions each year of approximately 612 births affected by NTDs following fortification, including 520 with spina bifida and 92 with anencephaly.²⁷

Our updated estimates of the costs of spina bifida are described elsewhere.⁴¹ We used a 3% discount rate to adjust projected lifetime costs in future years to the present value. The new OMB guidelines call for reporting results using both 3% and 7% discount rates.⁹ Results calculated with a 7% discount rate are available on request. In 2002 dollars, the lifetime total cost associated with a birth with spina bifida is estimated at \$636 000. Of this amount, \$279 000 represents lifetime direct costs, mostly medical, and does not include caregiving time costs. For anencephaly, the total cost is \$1 020 000, including \$1 014 000 in indirect costs⁴² and \$6000 in average hospital costs for births with anencephaly⁵ updated to 2002 prices.

We calculated a lower cost of fortification than in the prefortification analyses. It is not clear that food manufacturer analytic testing of enriched cereal-grain products is more expensive because of folic acid. Also, the price of bulk folic acid is lower than it was in the early 1990s. Specifically, the cost per ton of flour is one third lower than estimated in the California study (Peter Ranum, MS, oral communication, August 7, 2004). We estimated annual folic acid fortificant cost of \$2.2 million. Together with an annualized cost of \$800 000 for nutrition labels, this yields an es-

timate of fortification costs of \$3 million per year.

We calculated results for 2 scenarios. The base case scenario was based on assumptions that include attributing the observed reduction in NTDs to folic acid fortification, no cases of adverse effects from fortification, and fortification costs limited to fortificant and nutrition label changes. The worst-case scenario modified these assumptions by assuming that fortification is responsible for 80% of the observed reduction, that the number and cost of adverse effects was as predicted in the California study, and that annual fortification costs were twice what was calculated.

RESULTS

Our base case findings are summarized in Table 2. Following the CBA approach, the total economic benefit from reduction in the number of NTDs after folic acid fortification is estimated to be \$425 million per year. Subtracting fortification cost of \$3 million per year, the net monetary benefit is \$422 million. This compares with an estimate of \$94 million in the

California study. The magnitude of benefits is 4.5 times as great in the base case analysis as in the original study. The number of NTDs prevented was 2.0 times that predicted, and the per-birth cost was 1.7 times as great, as a result of both inflation and the use of a 3% discount rate in place of a 5% discount rate in the original study. Finally, the benefit estimate was 1.3 times greater because of the exclusion of costs of adverse effects and the lower estimate of fortification costs.

On the basis of the base case results, we estimated averted costs of care for children born with spina bifida of \$145 million per year. Subtracting \$3 million for fortification yields net cost savings of \$142 million per year, which compares with an estimate of \$5 million in cost savings from the CDC ex ante study.

Our worst-case scenario adjusted for 3 areas of uncertainty. One is the lack of information on potential cases of neurological damage secondary to untreated pernicious anemia. If adverse effects had occurred as modeled in the California analysis, our estimates of net

benefits and cost savings would be reduced by \$25 million each. A second area is the lack of information on other contributors to reduced NTDs. Assuming fortification is responsible for 80% of the observed decline, our estimates of net benefit and net cost savings would be reduced by \$85 million and \$29 million, respectively. Finally, our estimates of fortification costs may be too low. Manufacturers have added more folic acid to certain enriched foods, as shown by one laboratory analysis.²⁹ In addition, the cost of analytic testing has not been factored in. To allow for uncertainty in both areas, we doubled the estimated cost to \$6 million per year.

We calculated results for a worst-case scenario by setting all 3 parameters to their least favorable values. Under those assumptions, the net benefit was calculated to be \$312 million and the cost savings amounted to \$88 million. Although these numbers are substantially lower than our best-case estimates, they still greatly exceed the estimates prepared before fortification.

TABLE 2—Summary of Ex Post Economic Evaluation of Folic Acid Fortification at 140 µg/100 g, in 2002 dollars, Base Case Scenario

NTD	No. of NTDs Averted	Total Cost per NTD Birth (Direct Cost), \$	Total Benefit, \$ Millions	Net Benefit (Minus \$3 Million in Cost)	Total Direct Cost, \$ Millions	Cost Savings (Minus \$3 Million in Cost)
Spina bifida	520	636 000 (279 000)	331		145	
Anencephaly	92	1 020 000 (6000)	94		1	
Both	612		425	\$422m	146	\$143m

Note. NTD = neural tube defects, or cases of spina bifida and anencephaly; m = millions.



DISCUSSION

Ex post economic evaluations are underused in the regulatory arena. Because they are not required, few economic analyses are conducted after a regulation is adopted. Ex ante evaluations are necessarily on the basis of models and incomplete data, which require validation by subsequent studies.⁴³ In practice, certain policies turn out to be less effective and cost-beneficial than expected, whereas other policies, including folic acid fortification, generate more net benefits than anticipated.

Three independent economic evaluations conducted before 1996 all concluded that folic acid fortification at 140 µg of folic acid per 100 g of cereal-grain product would yield net economic benefits or cost savings.^{3–5} This conclusion was confirmed and strengthened by our postfortification analysis. Few public health interventions beyond immunization and injury prevention are cost saving.^{44,45} Folic acid fortification is exceptional in the relative magnitude of economic benefits.

The FDA choice of level of fortification was not made according to calculations of net economic benefit but on the safety standard that no group of people would be likely to be harmed. The FDA cited the California team's projection of 500 annual adverse effects from fortification at 140 µg of folic acid per 100 g of cereal-grain product but did not take this into account in projecting the costs and benefits of fortification.¹

The decrease in numbers of NTDs after fortification was greater than projected by the prefortification analyses. In part, this probably reflects a higher level of folic acid intakes than expected. It also reflects the conservative nature of the models used to project declines in numbers of NTDs. The validity of public health economic evaluations depends on the adequacy of epidemiological data and assumptions.

Estimates of net benefit depend on how costs and benefits are calculated. We have followed the COI method of valuation of health outcomes, which is a conservative approach to valuing health outcomes. Use of the WTP method could lead to a higher estimate of economic benefit of fortification, but WTP estimates for the prevention of congenital conditions are not available.

In our base case analysis, we did not include adverse health effects because of the absence of documentation that such effects have occurred with fortification. A study conducted in one US health care system found no change in diagnoses of anemia among people with vitamin B₁₂ deficiency after fortification.⁴⁶ If masking had occurred, one would expect fewer people with vitamin B₁₂ deficiency to have anemia. In addition, the prefortification projections may have overstated the risk by assuming that adverse effects would occur at intakes of 800 µg/day or 1 mg/day of total folate^{3,4} or 1 mg/day of folic acid.⁵ From the LOAEL of 5 mg/day reported by the IOM, one would expect no adverse effects to have resulted

from fortification. Because conclusive evidence requires additional research, we allowed for uncertainty. Our sensitivity analysis indicates that even if adverse effects had occurred as projected in the most pessimistic prefortification analysis, it would have little effect on estimates of net benefit.

In conclusion, folic acid fortification has proven to be a public health success in the United States and Canada, although an economic evaluation of fortification in Canada has yet to be conducted. The net benefit and cost savings surpass estimates prepared before fortification. By any measure, folic acid fortification provides a remarkable return on investment. Other industrialized countries could benefit by following the lead of the United States and Canada in adopting folic acid fortification of cereal-grain products. Furthermore, the benefits of fortification are not restricted to higher-income countries; fortification of wheat flour with folic acid in Chile has been associated with a 40% decrease in NTDs.⁴⁷ ■

About the Authors

Scott Grosse and Joseph Mulinare are with the Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, Atlanta, Ga. Norman Waitzman is with the Department of Economics, University of Utah, Salt Lake City. Patrick Romano is with the Division of General Medicine and Center for Health Services Research in Primary Care, University of California, Davis, Sacramento.

Requests for reprints should be sent to Scott Grosse, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Road, Mail Stop E-87, Atlanta, GA 30333 (e-mail: srosse@cdc.gov).

This article was accepted February 25, 2005.

Contributors

S. D. Grosse originated the study, directed all aspects of its implementation, and led the writing. All authors helped to conceptualize ideas, interpret findings, and review drafts of this article.

Acknowledgments

N. Waitzman received funding from the Centers for Disease Control and Prevention through an interagency personnel agreement (04IPA05219) with the University of Utah.

We acknowledge the encouragement and support of Dr. José Cordero, director of the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention (CDC), who requested that an economic evaluation of folic acid fortification be prepared. We acknowledge the contributions of Dr. Coleen Boyle, Director of the Division of Birth Defects and Developmental Disabilities at the CDC, who organized the symposium at which this analysis was presented and who reviewed multiple versions of this article and offered helpful insights. We also gratefully acknowledge helpful comments from David Hopkins and Godfrey Oakley, which helped to improve the focus of this article.

References

1. US Food and Drug Administration. Food standards: amendments of standards of identity for enriched grain products to require addition of folic acid. *Federal Register*. 1996;61:8781–8797.
2. Feinleib M, Beresford SA, Bowman BA, et al. Folate fortification for the prevention of birth defects: case study. *Am J Epidemiol*. 2001;154:S60–S69.
3. US Food and Drug Administration. Food standards: amendment of the standards of identity for enriched grain products to require addition of folic acid. *Federal Register*. 1993;58:53305–53312.
4. Romano PS, Waitzman NJ, Scheffler RM, Pi RD. Folic acid fortification of grain: an economic analysis. *Am J Public Health*. 1995;85:667–676.
5. Kelly AE, Haddix AC, Scanlon KS, Helmick CG, Mulinare J. Cost-effectiveness of strategies to prevent neural tube defects. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in*



Health and Medicine. New York, NY: Oxford University Press; 1996: 312–349.

6. US. Office of Management and Budget. Economic Analysis of Federal Regulations Under Executive Order 12866; 1996. Available at: <http://www.whitehouse.gov/omb/inforeg/riaguide.html>. Accessed September 23, 2004.
7. Haddix AC, Teutsch SM, Corso PS, eds. *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation*. 2nd ed. New York, NY: Oxford University Press; 2003.
8. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
9. US. Office of Management and Budget. *Circular A-4*; September 17, 2003. Available at: www.whitehouse.gov/omb/inforeg/circular_a4.pdf. Accessed September 23, 2004.
10. Krupnick AJ. *Valuing Health Outcomes: Policy Choices and Technical Issues*. Washington, DC: Resources for the Future; 2004.
11. Gaylor DW, Bolger PM, Schwetz BA. US. Food and Drug Administration perspective of the inclusion of effects of low-level exposures in safety and risk assessment. *Environ Health Perspect*. 1998;106(Suppl 1):391–394.
12. Neumann PJ. Why don't Americans use cost-effectiveness analysis? *Am J Manage Care*. 2004;10:308–312.
13. Laurence KM, James N, Miller MH, Tennant GB, Campbell H. Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. *Br Med J (Clin Res Ed)*. 1981;282:1509–1511.
14. Smithells RW, Nevin NC, Seller MJ, et al. Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet*. 1983;1:1027–1031.
15. Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. *JAMA*. 1988;260:3141–3145.
16. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folate acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *JAMA*. 1989;262:2847–2852.
17. Bower C, Stanley FJ. Periconceptional vitamin supplementation and neural tube defects; evidence from a case-control study in Western Australia and a review of recent publications. *J Epidemiol Community Health*. 1992;46:157–161.
18. Medical Research Council Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*. 1991;338:131–137.
19. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med*. 1992;327:1832–1835.
20. US Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Morb Mortal Wkly Rep*. 1992;41:1–7.
21. Rosenberg KD, Gelow JM, Sandoval AP. Pregnancy intendedness and the use of periconceptional folic acid. *Pediatrics*. 2003;111:1142–1145.
22. Oakley GP Jr. Inertia on folic acid fortification: public health malpractice. *Teratology*. 2002;66:44–54.
23. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin and Choline*. Washington, DC: National Academy Press; 1998.
24. US Food and Drug Administration. Food labeling: health claims and label statements, folate and neural tube defects. *Federal Register*. 1993;58:53254–53295.
25. US Food and Drug Administration. Food labeling: health claims and label statements, folate and neural tube defects. *Federal Register*. 1996;61:8752–8780.
26. Waitzman NJ, Scheffler RM, Romano PS. *The Cost of Birth Defects*. Lanham, MD: University Press of America; 1996.
27. Williams LJ, Mai CT, Edmonds LD, et al. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. *Teratology*. 2002;66:33–39.
28. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. *Lancet*. 2001;358:2069–2073.
29. Rader JL, Weaver CM, Angyal G. Total folate in enriched cereal-grain products in the United States following fortification. *Food Chemistry*. 2000;70:275–289.
30. US Centers for Disease Control and Prevention. Knowledge and use of folic acid by women of childbearing age—United States, 1995 and 1998. *MMWR Morb Mortal Wkly Rep*. 1999;48:325–327.
31. US Centers for Disease Control and Prevention. Use of vitamins containing folic acid among women of childbearing age—United States, 2004. *MMWR Morb Mortal Wkly Rep*. 2004;53:847–850.
32. Daly S, Mills JL, Molloy AM, et al. Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. *Lancet*. 1997;350:1666–1669.
33. Mills JL. Fortification of foods with folic acid—how much is enough? *N Engl J Med*. 2000;342:1442–1445.
34. De Wals P, Rusen ID, Lee NS, Morin P, Niyonsenga T. Trend in prevalence of neural tube defects in Quebec. *Birth Defects Res Part A Clin Mol Teratol*. 2003;67:919–923.
35. Ray JG, Meier C, Vermeulen MJ, Boss S, Wyatt PR, Cole DE. Association of neural tube defects and folic acid food fortification in Canada. *Lancet*. 2002;360:2047–2048.
36. Gucciardi E, Pietrusiak MA, Reynolds DL, Rouleau J. Incidence of neural tube defects in Ontario, 1986–1999. *CMAJ*. 2002;167:237–240.
37. Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *CMAJ*. 2002;167:241–245.
38. Liu S, West R, Randell E, et al. A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects. *BMC Pregnancy Childbirth*. 2004;4:20.
39. Berry RJ, Li Z, Erickson JD, Li S, et al. Prevention of neural-tube defects with folic acid in China. China-US Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med*. 1999;341:1485–1490.
40. Botto LD, Olney RS, Erickson JD. Vitamin supplements and the risk for congenital anomalies other than neural tube defects. *Am J Med Genet*. 2004;125C:12–21.
41. Waitzman NJ, Romano PS, Grosse SD. Half-life of cost of illness estimates: the case of spina bifida. In: Wyszynski DF, ed. *Neural Tube Defects: From Origin to Treatment*. New York, NY: Oxford University Press; 2005:342–351.
42. Grosse SD. Productivity loss tables (Appendix I). In: Haddix AC, Teutsch SM, Corso PS, eds. *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation*. 2nd ed. New York, NY: Oxford University Press; 2003: 245–257.
43. Thompson KM, Segui-Gomez M, Graham JD. Validating benefit and cost estimates: the case of airbag regulation. *Risk Anal*. 2002;22:803–811.
44. Coffield AB, Maciosek MV, McGinnis JM, et al. Priorities among recommended clinical preventive services. *Am J Prev Med*. 2001;21:1–9.
45. Miller TR, Levy DT. Cost-outcome analysis in injury prevention and control: eighty-four recent estimates for the United States. *Med Care*. 2000;38:562–582.
46. Mills JL, Von Kohorn I, Conley MR, et al. Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr*. 2003;77:1474–1477.
47. Hertrampf E, Cortes F. Folic acid fortification of wheat flour: Chile. *Nutr Rev*. 2004;62:S44–S48.