Folic Acid Fortification: Fact and Folly

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If one were looking for a test of the effectiveness of the new significant scientific agreement standard specified in the 1990 Nutrition Labeling and Education Act, no one would have to look much farther than the folic acid story to find evidence that less can be more in the rapidly changing landscape of modern science. In the case of folic acid, the new scientific standard, feared by so many, actually worked not only to lessen the bureaucratic load, but in this case also appears to have conferred significant public health benefits. Originally, the effort was directed at women in their reproductive years to lessen their dangers of giving birth to a child with neural tube defects, including spina bifida. Scientists increasingly suspect, however, that a greater consumption of folic acid may also reduce the danger of Alzheimer's disease, and also offer some protective effects against certain kinds of cancer as well as heart disease. These added benefits appear to make the folic acid fortification decision that much more important historically. The only folly comes in when one refers back to what turns out to be the often appallingly poor and lopsided press coverage afforded this important public health issue. This issue was much less about turf and the omnipresent battle between the vigorous purveyors of vitamins and the heroic defenders of natural foods than the press perceived at the time. It was far more of a scientific struggle over research rigor complicated by a mandate to implement the desires of Congress as they had been expressed through some very new and seemingly complicated laws. Complicated legal and scientific issues, however, rarely command headlines.

Linking Folic Acid with Prenatal Health

In the 1970s, it had become possible to fortify vitamins with folic acid, and there were some recommendations that flour be fortified with additional folic acid. The former was adopted with some limits, and the latter abandoned. By the late 80s and early 90s, the National Research Council had recommended, and FDA was considering, lowering the RDA from 400 mg. to 200 mg. per day. In 1990, the National Academy of Science went one step further. While recommending additional studies on folate intake prior to pregnancy, it suggested that "it would be desirable for women of childbearing years to follow dietary guidelines . . . increased consumption of fruits, vegetables, whole grains and cereals." This report, according to almost all observers pitted supplement makers against nutritionists. The recommendation against the routine use of multivitamins in pregnancy would have reversed standard pre-natal practice and in the words of one newsletter writer, "the toes of the nutrient supplement industry had been stepped on and we all heard the ouch."

Folic acid fortification, for all practical purposes, was not even on the regulatory horizon when it was first included in the 1990 Nutrition Labeling and Education Act (NLEA). FDA scientists at the time felt that the charge to consider the link between folic acid and neural tube defects

literally came "out of the blue." Later, they concluded it probably started with a science workshop hosted by CDC in the late 80s in which unpublished data on folic acid and neural tube defects were presented and seized upon by the supplement industry. However it arrived on the scene as an issue, it soon became an unusually contentious one. As Dr. Beth Yetley so honestly stated at a meeting of the Folic Acid Subcommittee of the FDA's Food Advisory Committee in 1993, "we truly have been on the cutting edge of science and public policy as we've worked through this health claim procedure [for folic acid]. NLEA allowed health claims on foods provided that the nutritional claim for a food substance could be substantiated and was related to a disease or health related condition. One of the ten claims that the agency was told to evaluate was one linking folic acid with a reduction in neural tube defects (ntd's).

The Movement for New Nutritional Standards

While FDA was frantically looking at the admittedly meager and inconclusive scientific evidence on the issue, a major study was published in the Lancet. The article analyzed in detail the results of a multi-center, multi-national randomized prevention trial by the British Medical Research Council (MRC) Vitamin Study Group. The study had begun in 1983 and was halted in 1991, when it was felt that the results warranted offering folic acid supplementation to all study participants. The study focused on women who had had a previous pregnancy with an infant or fetus with a neural tube abnormality and who were planning another pregnancy. One group was given 4 mg of folic acid, the second group a multivitamin with 4 mg of folic acid, the third group was given no supplementation, while the final group received a multi-vitamin without folic acid. Folic acid supplementation was associated in this study with a 71% reduction in neural tube defects. The study also demonstrated that such results were achieved only when supplementation began before conception and continued through the first three months of the pregnancy. These and other similar findings were presented at a meeting at the Centers for Disease Control (CDC) in September, 1991 at a conference on "Vitamins, Spina Bifida, and Anencephaly." The CDC relied on these findings to issue a formal recommendation. Women who had previously had an infant or fetus with spina bifida, anencephaly, or encephalocele were urged to take 4 mg. of folic acid supplementation per day. This recommendation was not particularly easy to implement. One mg. folic acid tablets were available only by prescription; there were no New Drug Applications (NDA) for folic acid to prevent ntd's; and CDC warned that women should not try and attain the 4 mg dose with OTC vitamins because of the danger that they would reach teratogenic and toxic levels of vitamins A and D. A few scientists at the meeting did seem to catch a glimpse of the enormity of the task at hand. One noted that it would have to be presumed that "all women are pregnant unless proven otherwise," necessitating supplementation for thirty years or more. Others questioned how practical it would be to prevent ntd's before pregnancy in women when the situation was vastly complicated by a very large number or unplanned pregnancies each year.

At the 1991 CDC Conference on "Vitamins, Spina Bifida, and Anencephaly" it became generally accepted that some women required more folic acid before and during early pregnancy to prevent neural tube defects . As one scientist reasoned, "it could be chance, but it's confirmatory of the other data, so folic acid does something." The sticking point was how best to provide it for them: reformulate prescription prenatal vitamins and/or over-the-counter supplements, make folic acid a separate prenatal vitamin, fortify the food supply for everyone? David Kessler called this scientific and policy matter "one of the more difficult issues" he confronted as Commissioner.

In November, 1991, the Federation of American Societies for Experimental Biology (FASEB) issued their FDA-contracted report. "Folic Acid and Neural Tube Defects" acknowledging that the studies to date had failed to "positively conclude that it's the folic acid" which prevented ntds. However, the study's author, Daphne Roe, M.D. rebuked a 1990 report of the Food and Nutrition Board of the Institute of Medicine (IOM). Nutrition During Pregnancy, Part II, Nutrient Supplements of the Subcommittee on Dietary Intake and Nutrient Supplements. The report had concluded that periconceptual use of vitamins for prevention of ntds was "unjustified." She also took issue with the National Academy of Science's (NAS) Report on Nutrition and Pregnancy that also found "no link" between folate deficiency in pregnant women and ntds in their offspring. Given the results of the MRC Vitamin Study Research Groups' 1991 article, Roe concluded that the conclusions reached by the IOM and NAS could "no longer be generally accepted."

The Struggle for Regulatory Consensus

It was perhaps unfortunate that FDA was forced under the tight statutory deadlines imposed by the 1990 Nutrition Labeling and Education Act (NLEA) to publish its proposed rules mandated for consideration under NLEA at just this juncture in the scientific debate. The November 1991 proposals provoked a widespread outcry when FDA rejected three of the first four proposed claims, including that for folic acid and the prevention of ntd's. The agency's folic acid decision, however, was accompanied by a caveat: it was merely a "tentative conclusion" while the results of the MRC study were being evaluated. Although FDA scientists did believe that the 1991 report of the British MRC study supported a relationship between folic acid intake and reduction of risk for recurrence of ntds, they also considered the 4 mg. per day necessary to produce these results to be pharmacologic, or drug doses. FDA did not believe that there was evidence of significant scientific agreement that folic acid at dietary intake levels could reduce ntd risks. High intakes of folic acid, too, might pose their own risks and these were largely unknown. FDA itself limited the folic acid content of fortified foods, formulas, and non-prescription vitamin supplements to no more than 1 mg. because it was known that more than 5 mg. a day can mask vitamin B12 deficiency. FDA also publicly criticized the FASEB study as "frequently inconsistent," saying that it had "failed to focus on the specific relationship of folic acid to NTDs and on differences in risk between recurrences v. occurrences of ntd pregnancies."

FDA's scientific reasoning was sound; however, the political climate was particularly harsh, and FDA resources were stretched too thin on too many fronts. FDA had announced soon after the enactment of NLEA that it would evaluate health claims for foods and those for dietary supplements in the same fashion, holding each to the same standard of significant scientific agreement. Many apparently concluded from that that the agency would be averse to claims for both. But that was a shortsighted interpretation. A typical response, for example, was that of Better Nutrition Newsletter whose editor concluded that "FDA's negative position on food supplements is rather mystifying." In this context, NLEA's lustre could not help but be tarnished by these early rejections, which were later challenged in court by those claiming that they violated First Amendment free speech rights. FDA's Dr. Beth Yetley emphasizes, however, that "FDA was looking at specifics" in evaluating these first health claims, and "not fighting the overall tenet" of the NLEA legislation, which it enthusiastically supported. Complicating an already complicated problem, folate measurement methodology at this time was not particularly

accurate. Serum folate and red blood folate had some crude measuring methods, but folate measurements in foods required considerable refinement before they could be considered accurate.

Fueling the fire was a May 1992 editorial by Walter C. Willett, M.D. in the American Journal of Public Health, entitled "Folic Acid and Neural Tube Defect: Can't We Come to Closure?" Willett expressed the growing frustration of many when he charged that "the unwillingness of the official U.S. agencies to generalize even slightly from the conditions of the Medical Research Council Study" was "most disturbing." The current evidence, he said, provided an excellent example of "how data from observational epidemiologic and randomized trials can be most informative when viewed as being complementary." He too criticized the NAC report on Nutrition in Pregnancy and he criticized CDC officials for "not going far enough" on the issue, even though in February 1992, CDC's Director of the National Center for Environmental Health and Injury Control, William Roper, had proposed the solution ultimately adopted. "Fortification," he said, "should be the long term goal," but acknowledged "a short term reliance on dietary supplements" might be required. FDA officials, Willett felt, should have considered a label claim for folic acid and should have rejected outright any proposal to reduce the RDA from .4 to .18 mg. folic acid. In the same month, a new term was coined: "nutraceutical."

The Werler Study

In June, 1992, FDA re-opened its comment period on the final rules for 30 days after the agency learned that the CDC was holding another conference on folic acid. FDA held hope that the meeting might shed new light "on the relationship between the ingestion of folic acid and neural tube defects," but it was concerned about the use of unpublished studies. FDA's mandate under NLEA required that the agency employ information available on the public docket.

The situation changed quickly after this CDC meeting. In August and September 1992, FDA reviewed results obtained from two additional, unpublished studies, and worked closely with authors and journals publishing them to ensure that the results were made public early. The first, a Hungarian research study, showed a reduced risk of ntd's in women consuming .8 mg. of folic acid as part of a multivitamin/mineral supplement. The study had been conducted with a sample of women in the general population without a previous history of an ntd pregnancy. The second study was a case control study of women in the general population of Boston, Toronto, and Philadelphia and was referred to as the "Werler study." This study suggested that .4 mg. of folic acid daily from multivitamin/mineral supplements was associated with a reduced risk of ntd. It also suggested that a diet adequate in folate with more than .25 mg. daily was protective. The new preponderance of scientific evidence on folic acid created a platform from which the Public Health Service (PHS) spoke on September 14, 1992. PHS formally recognized the link between folic acid intake and ntd's as a compelling public health issue. It recommended that all women of childbearing age should have adequate folate intakes (.4 mg. daily) throughout their childbearing years, but warned that the total intakes should not exceed 1 mg. PHS recognized three options to meet its own recommendation: educational programs to improve food selection; food fortification; and supplement use. PHS acknowledged, however, that there were still many unresolved issues. The lowest effective dose was unknown, for example, and there were other

safety issues which would have to be resolved before PHS could take action on the fortification and health claims issues.

FDA had the significant scientific agreement it needed to move forward, and the agency began to lean toward supporting food fortification. At a 1993 March of Dimes meeting, however, David Kessler cautioned his audience that "before we fortify the food supply for 250 million Americans, we have to make sure we get it right."

Weighing the Risks and Benefits of Fortification

In light of the PHS recommendations on folic acid intake, FDA began to consider the merits of food fortification. It could enhance efforts to help Americans choose good foods rather than rely on supplements. Supplements, due their high costs, would not resolve the problem. According to concerned nutrition experts, supplements would have discriminated against the poorest women. in our society, a group of women who may be at the highest risk for neural tube defects, with the least resources for coping with the birth of a child with spina bifida. Finally, and most importantly, fortification was felt to be the best way to insure that women of child-bearing age received supplementation in the months leading up pregnancy and in the critical window when a woman might not know that she was pregnant, but the neural tube was being established.

Opponents, however, were numerous. Irwin Rosenberg, M.D., Director of the USDA Human Nutrition Center on Aging, for example, opposed the move towards fortification. He predicted that the PHS announcement would "put enormous pressure on the FDA to show consistency in its policy vis a vis the folate and neural tube health claim on foods" and "destroy the scientific basis for RDA's in this country." Moreover, he was concerned about the effects of fortification on the elderly since their findings showed that 20-25% of the elderly had low or borderline vitamin B12 stores and malabsorption. It was well-known that folate can mask signs of vitamin B12 deficiencies, a significant health concern throughout the fortification debates.

Implementing NLEA

On October 30, 1992, an act called the Dietary Supplement Act (DSA) was enacted which preceded the Dietary Supplement Health and Education Act (DSHEA) implementation of the 1990 Nutrition Labeling and Education Act (NLEA) until November 1993. Under DSA, however, FDA could continue to consider and grant health claims for conventional foods, using the significant scientific agreement standard NLEA specified. On November 5, 1992, FDA announced that it would convene an advisory committee to provide recommendations on the target population for a folic acid neural tube defect health claim, and several other related issues related to folic acid dietary supplementation. When the Folic Acid Subcommittee initially met, it spent some time criticizing the methodology of the most recent folic acid studies, but in the end, the committee agreed that "the weight of evidence now supported significant scientific agreement for the relationship between folic acid and ntds at dietary intake levels." They had, however, unresolved concerns about the safety of potentially high intake levels of folic acid. In 1993, FDA had to publish final regulations on the ten initial health claims mandated under NLEA. The 1993 rule on folic acid rejected a health claim at that time, but made it clear that this decision would be reconsidered in conjunction with efforts to implement the PHS

recommendation, including a resolution of safety issues, and a consideration of fortification of selected foods. Dr. Beth Yetley, of the FDA Center for Food Safety and Applied Nutrition (CFSAN) and Director of the Office of Dietary Supplements, later noted that safety issues had become "a burden" in approving health claims. "We could not approve a health claim for which we could not assure its safe implementation."

Publicity swirled around the 1993 final rule and its refusal to allow a health claim for folic acid, while the larger significance of the committee's recommendation went unappreciated. The Folic Acid subcommittee expressed support for fortification. That was the key element in all that followed. As *Time* reported, the subcommittee had expressed concern for the fact that "most pregnancies are unplanned" in its decision to support food fortification.

This was a momentous action for an otherwise conservative group of nutritionists and nutrition scientists. This would be the first highly significant food fortification act since the 1940s and many of the subcommittee members were aware that such action would be historic in the field of nutrition. National enrichment and fortification efforts are public health initiatives undertaken only in light of significant scientific findings relating a specific vitamin deficiency to a specific disease condition. Iodine had been added to salt in 1924 to prevent goiter, and other expressions of iodine deficiency. In the 1930s vitamin D was added to milk to prevent rickets and aid in calcium and phosphorus absorption. From 1938 through 1943, an enrichment formula was developed for flours and breads that included thiamin to prevent beriberi, niacin to prevent pellagra, riboflavin to assist in B6 and niacin utilization, and iron to prevent anemia. Later, vitamin A was added to low and non-fat dairy products and lysine has been added to a few foods to enhance their protein content, but such additions had been few and far between in the aftermath of the impressive World War II initiatives.

Public support for a fortification effort began to grow. The Center for Science in the Public Interest (CSPI) supported FDA's final rule, and urged FDA to "carefully consider fortifying the food supply." In our view, wrote CSPI, "only fortification would deliver adequate levels of folic acid to all segments of the target population on a daily basis for extended periods of time." David Smith, of the Texas Department of Health, wrote FDA to make it aware of the positive results his department had achieved with prenatal vitamins used to reduce the incidence of ntd's in southern Texas. His department supported not only fortification, but advocated delivering a strong health message as well.

Revisiting Fortification Regulations

FDA reconvened its Folic Acid subcommittee in April 1993 to try and resolve many of the stumbling blocks it had encountered, but not resolved in November 1992. At that time, FDA had considered health claims as it struggled to meet the NLEA deadline for its final rule. Many of the subcommittee members were initially skeptical of any health claim for folic acid. In part, this was because with the science at hand, they felt an accurate claim for folic acid would have to point out both the benefits and the potential risks from consuming more than 1 mg. daily. One member noted that it would be difficult to "warn the population not to eat too many vegetables if you go and eat cereal." Another was concerned about kids whose folic acid intake might rise dramatically and those who might consider a warning and decide that "between my frosted flakes

and my broccoli, I'll keep up with my frosted flakes and drop the broccoli." In part, however, the subcommittee members were deeply divided on the merits of health claims for foods in general. Dr. Joan D. Gussow, for example, spoke for many in saying, "Health claims in general on foods are a bad idea because they focus on single nutrients, and since I believe that combinations of foods are what build health, not nutrients, I'm philosophically opposed to health claims. I think that [NLEA] was a mistake to allow them." Marion Nestle, editor of the Surgeon General's report Healthy People 2000, questioned the accuracy of the food composition database the committee was using, and concluded that "what the data do show at this point is that they establish a basis for a major national campaign to promote consumption of fruits, vegetables, and grains." The subcommittee resolved its concern over fundamental nutritional philosophy by polling its members about their opinion on health claims: 8 opposed; 9 supporting, and 5 abstaining. This simple poll affirmed their professional stances for the record, and cleared the way for the committee to get down to the business of considering folic acid claims in the context of national policy.

Given the national environment, most of the committee members took a pragmatic stance on folic acid . Dr. Peter Greenwald, Director of the National Cancer Institute (NCI) at NIH, reminded them that Congress had already sensed a broad public interest in the relationship between food and health, and that the public wanted good information on the subject. Given that, he said, "avoiding the issue doesn't seem to be in the best public interest, I think it may be better to give the best information that we can give in an understandable fashion." Greenwald also noted that CDC had studied the vitamin B12 deficiency-masking problem, saying that he thought this concern might be overstated. He reminded the subcommittee that they need not act in a vacuum. Their folic acid decisions were part of a Department of Health and Human Services (DHHS) wide agenda and "must be associated with a strong research agenda that DHHS, CDC, NIH, and FDA would undertake including attention to the effects on children and the potential benefits against chronic diseases such as heart disease and cancer . . . and the role of folate [consumption] as a risk factor in colorectal cancer, cervical cancer, and pre-cancerous lesions related to lung cancer."

Evaluating Nutritional Health Claims

In October 1993, in separate rulemaking, FDA proposed a health claim for folic acid and neural tube defects. Under the proposal, health claims would be permitted on foods containing .04 mg. or more of folic acid per serving. FDA proposed amending the standards of identity for cereal grains labeled as "enriched" to require mandatory addition of folic acid at .14 mg. Dietary supplements would retain their levels of .4 mg. per daily dose. Breakfast cereals would contain .1 mg. per serving and folic acid would be required for enriched cereal grain products including flour, cornmeal and rice. To assist PHS in implementing its recommendations, FDA proposed limiting the foods to which folic acid could be added. Combined with limitations on levels permitted in foods, FDA felt this policy would resolve outstanding safety concerns.

Implementation, however was a tricky affair. FDA had learned a lot about fortification over the years. Most especially, officials had learned that in matters of fortification "less" frequently provides "more" public health coverage and that lower levels of fortification often make the most impact. This would be especially true, officials felt, for folate. Folate is distributed ubiquitously

in foods and FDA did not want to do anything to discourage consumption of foods such as bread in multiple servings per day. The requirements for other health claims on food required that the food be a "high" source of the nutrient, however, and few foods carried 20% or more of the Daily Value (DV) for folate. FDA responded by proposing a lower minimum content criterion for the folate health claim: 10% DV. FDA also advised that folic acid claims avoid use of the term "prevents" and instead use "reduce the risk of." FDA's proposed rule on health claims for folic acid and neural tube defects became final on December 31, 1993. It was the eighth such health claim approved under NLEA by FDA [saturated fat/cholesterol and heart disease; total fat and cancer; sodium and hypertension; calcium and osteoporosis; antioxidant vitamins in fruits, vegetables and grains and cancer; dietary fiber and heart disease; dietary fiber and cancer]. Under the proposal, if a food product contained more than 25% of the Recommended Daily Intake (RDI) for folic acid, it would be required to state that 1 mg. folate is the established safe upper limit of consumption. Moreover, if a product carried more than 100% of the RDI for vitamin A or D, then it could not carry a claim. For regulators, this seemed reasonably comprehensive and straightforward. Others felt differently. At the 1993 subcommittee hearings Dr. Alving warned that although the labeling met the Congressional and FDA requirements, it might not be effective for the consumer. "Right now," he remarked, "I think it kind of takes about a college course in nutrition to begin to get through it, assuming one has the time. So I think a lot of effort should be put into trying to make this consumer-usable."

The Final Rule

On March 5, 1996, FDA's final rule on folic acid fortification was published. By the time the ruling was fully implemented, the mounting evidence of its effectiveness had silenced most of its critics. In 1993, Durk Pearson and Sandy Shaw, co-authors of a best-selling book *Life Extension: A Practical Scientific Approach* (New York: Warner Books, 1982) and advocates of the liberal use of vitamins and other dietary supplements, had made the only broad-based criticism of folic acid fortification. Adapting the arguments and rhetorical style of the anti-fluoridationists of the last century, they wrote that "Pearson, Shaw, and quite likely the entire medical profession in the free world, consider it unethical to medicate conscious and mentally competent adults without first obtaining that adult's informed consent." Far more significant, however, were the practical criticisms heard in the beginning of the effort charging that the fortification levels employed were inadequate. By the time the rule issued, preliminary evidence already indicated that these smaller levels of fortification had achieved their purpose and so far appeared to have avoided the pitfalls of masking vitamin B-12 related anemia. According to Dr. Beth Yetley, FDA's past experience with fortification had been the agency's guide. Regulators had previously found that small amounts of fortification often yielded much larger than anticipated protective results. Although they will continue to monitor health effects attributed to folic acid fortification, the overall effort seems to have been a true victory in the battle to enhance the health of future generations of babies.