DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 91N-0100]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements; Folic Acid and Neural Tube Defects

Agency: Food and Drug Administration, HHS.
Action: Final Rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing its decision not to authorize a health claim for folic acid and neural tube defects at this time. However, consistent with the recently announced recommendations of the U.S. Public Health Service (PHS) that all women of childbearing age in the United States consume 0.4 milligram (mg) (400 micrograms (pg)) of folic acid daily to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects. FDA plans to work expeditiously to authorize a claim, if appropriate. At that time the PHS identified several issues that remain outstanding, including the appropriate level of folic acid in food and safety concerns regarding increased intakes of folic acid. Given the significance of neural tube defects and the PHS recommendation, the agency is continuing to address the issues about folic acid. FDA recently convened an advisory committee to consider the outstanding concerns (57 FR 52781, November 5,1992). The advisory committee provided recommendations to the agency on the following issues: (1) What is the target population for a folic acid neural tube defect health claim? (2) How does the information available on the effective level of intake affect options for implementation? (3) What safety concerns for the target population and for persons in the general population must be addressed? and (4) If a claim is authorized, what is the most appropriate method for presenting it to the target population? The advisory committee's recommendations are currently under FDA review.

EFFECTIVE DATE: May 8, 1993.

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SUPPLEMENTARY INFORMATION:

I. Background

A. Procedural Status

In the **Federal Register** of November 27, 1991 (56 FR 60610), FDA proposed not to authorize the use on the label and labeling of foods, including dietary supplements, of health claims relating to an association between folic acid and the reduction in risk of neural tube birth defects. The agency issued this proposal in response to the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) (Pub. L. 101-535). The agency tentatively found that the available scientific evidence showed that daily periconceptional use of 4 mg (4,000 µg) of folic acid, an amount that exceeds the level of 0.4 mg (400 µg) per (/) day permitted under the current food additive regulation (21 CFR 172.345), was needed for reduction in risk of neural tube birth defects in women at high risk of this complication because of a previously affected pregnancy. The agency also tentatively concluded at that time that there was not significant scientific agreement that periconceptional supplementation with doses of folic acid lower than 4 mg/day would significantly reduce the risk of neural tube defects in women of childbearing age in the general U.S. population, who are at much lower risk of an occurrence of this complication.

In September 1992, following an open meeting sponsored by the Centers for Disease Control (CDC) in Atlanta, GA (57 FR 29323) and based on additional reviews of existing data and on new scientific data, the PHS recommended that all women of childbearing age in the United States consume 0.4 mg (400 ug) of folic acid daily to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects (Ref. 1). In discussing this recommendation, the PHS raised several issues that directly bear on FDA's responsibilities under the Food, Drug, and Cosmetic Act (the act) and the agency's pending rulemaking on whether to authorize a health claim regarding folic acid and neural tube defects. These issues include: (1) Identifying the population at risk, (2) considerations of appropriate level of intake with respect to options for implementation, (3) magnitude of benefit, (4) safety considerations, and (5) identifying the best approach for implementing the recommendation.

The 1990 amendments, in section 3(b)(1)(A)(x), direct FDA to consider whether to grant a health claim for dietary supplements on the effects of folic acid on neural tube defects. Section 3(b)(1)(A)(x) of the 1990 amendments directs the agency to make this judgment based on the standard that FDA is to establish for determining the reliability of health claims for dietary supplements of vitamins, minerals, herbs, and other nutritional substances under section 403(r)(5)(D) of the act (21 U.S.C 343(r)(5)(D)). In its November 27,1991 proposal, FDA proposed to adopt the standard that the 1990 amendments provide for conventional foods, which is set forth in section 403(r)(3)(B)(i) of the act, as the standard for dietary supplements. Given this fact, and the fact that folic acid is found in numerous conventional foods as well as in dietary supplements, FDA broadened its inquiry to a determination as to whether it should grant a health claim on folic acid and neural tube defects on any foods.

On October 6, 1992, Congress passed the Dietary Supplement Act of 1992 (the DS Act) which prohibits implementation of the 1990 amendments with respect to dietary supplements of vitamins, minerals, herbs, or other similar nutritional supplements before December 15, 1993. Under the DS Act, FDA may grant health claims for foods, including dietary supplements, using the significant scientific agreement standard specified in section 403(r)(3)(B)(i) of the act. Given this fact and given the breadth of FDA's November 27, 1991 proposal, which included conventional foods as well as dietary supplements, FDA has decided to move forward to determine whether it can authorize a health claim under section 403(r)(3)(B)(i) of the act for folic acid and neural tube defects by resolving the outstanding issues identified in the PHS recommendation (Ref. 1) and in comments to the November 1991 proposal.

With its recommendation, PHS made comments that identified several possible approaches for the delivery of folic acid in the dosage recommended to the general population: (a) Improvement of dietary habits, (b) fortification of the U.S. food supply; and (c) use of dietary supplements. PHS stated that FDA, in deciding whether to authorize a health claim, will have to determine which approaches will best achieve the goal of increasing folic acid intake, while ensuring that potential risks created by overfortification of food with folic acid, and overconsumption of this substance, do not occur.

FDA recognizes that fortification of a wide variety of foods could occur following authorization of a health claim, and that such fortification could lead to a significant increase in the

intake of folic acid by women in their childbearing years as well as by other portions of the general population. Such an increase would bring with it certain risks. The most widely recognized adverse effect of high intakes of folic acid is the potential for progressive neurologic damage resulting from undiagnosed or masked vitamin B_{12} deficiency. This potential risk was recognized by PHS, which stated that because the effects of higher intakes of folic acid are not well known but include complicating the diagnosis of vitamin B_{12} deficiency, care should be taken to keep total folate consumption at less than 1 mg (1,000 pg)/day, except under the supervision of a physician (Ref.1).

FDA's current food additive regulation for folic acid (21 CFR 172.345) does not include limits on the fortification of specific commodities, and thus, a wide variety of foods could be fortified with folic acid to provide up to 400 μg/day from each source. Such fortification could lead to individual intakes in the range of 3 to 5 mg (3,000 to 5,000 μg) or more of folic acid per day. Thus, there is a significant question as to whether a health claim relating intake of folic acid and reduced risk of neural tube defects, if approved, could be implemented safely.

The requirement that substances eligible for health claims be safe and lawful is included in the final rule for health claims on foods (see General Requirements for Health Claims for Foods, published elsewhere in this **Federal Register**). Sections of the Federal Food, Drug, and Cosmetic Act (the act) enacted by the 1990 amendments cannot be implemented independently of the remaining portions of the act. The act must be considered as a whole, and FDA's responsibility for ensuring the safety of foods is explicitly provided for in other sections of the act (see sections 201(s), 402(a)(1) and (a)(2), and 409, as well as 403(r)(3)(A)(ii) of the act (21 U.S.C. 321, 342(a)(1) and (a)(2), 348, 343(r)(3)(A)(ii))).

The process by which FDA fulfills its responsibilities under the act will require rulemaking. While this process is underway, and before FDA can issue final regulations on fortification of food with folic acid and permissible health claims on foods that contain folic acid, further food fortification with folic acid would be inappropriate; and no health claims should be made (Ref. 1). FDA notes that the PHS recommendation clearly stated that there were risks attendant on overconsumption of folic acid.

B. Neural Tube Defects: Public Health Aspects

As discussed in the proposal (56 FR 60610), several specific malformations of the central nervous system are referred to as "neural tube defects" because the brain and spinal cord develop within the neural tube. The neural tube forms between the 18th and 20th days of pregnancy and closes between the 24th and 27th days. Anencephalus and spina bifida are serious birth defects and account for about 90 percent of neural tube defects. The majority of children with spina bifida survive and have substantial physical disabilities. Most anencephalic infants are stillborn or die shortly after birth. The minimum number of neural tube defect births in the United States is 2,500. This is an underestimate of neural tube defect pregnancies, however, because it does not include neural tube defect pregnancies identified by prenatal diagnosis and electively terminated. Recent data from state-based birth defects surveillance systems show decreasing trends for spina bifida from 1983 to 1990. The combined state rate is 4.6 cases of spina bifida per 10,000 live births (0.046 percent) (Ref. 2).

The multifactorial nature of neural tube birth defects is well recognized (56 FR 60610 at 60611). The single greatest risk factor currently recognized is having a previous neural tube defect-affected pregnancy. Prevalence rates of neural tube defects at birth have been reported to vary with a wide range of factors, including: Genetics, geography, socioeconomic status, maternal birth cohort, month of conception, race, nutrition, and maternal health including maternal age and reproductive history. Certain geographic areas may have, for unknown reasons, considerably higher rates than other areas. For example, a cluster of anencephalic deliveries occurred in the Brownsville, TX area between 1989 and 1991. Investigations of potential causes, including environmental contamination and other factors, are ongoing in this area (Ref. 3).

Maternal health (e.g., febrile illness) and maternal use of certain drugs (e.g., the anticonvulsant drug valproic acid) also contribute to risk of neural tube birth defects. There is an increased incidence of malformations, including neural tube defects, among infants of diabetic mothers. Carriership for an inborn error of homocysteine metabolism has been proposed as a risk factor for having an infant with a neural tube defect (Ref. 4). Poor maternal nutrition, which is among a number of factors associated with poverty, may increase the risk for neural tube defects. A recent case-control study of the cluster of anencephalic deliveries in the Brownsville, TX area found that women with less than a high school education were more than twice as likely to have an infant with a neural tube defect as were women who had finished high school (Ref. 3). This observation correlates with poverty as a known risk factor for neural tube birth defects (Ref. 3).

C. Folic Acid: Regulatory History

1. Drug regulation

The agency evaluated the use of folic acid as a drug in the **Federal Register** of April 9, 1971 (36 FR 6843) in response to reports received from the National Academy of Sciences on the therapeutic uses of folic acid. The agency concluded that folic acid administered orally or parenterally is effective for the treatment of megaloblastic anemias of tropical and nontropical sprue, those of nutritional origin, and those that may occur during pregnancy, infancy, and childhood. The agency found that administration of folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient because such treatment may mask the symptoms of vitamin B_{12} deficiency.

In the presence of excess folic acid and inadequate vitamin B_{12} the anemia of vitamin B_{12} deficiency may not develop, but severe and irreversible nerve damage may continue. Because the anemia of vitamin B_{12} deficiency is frequently the earliest clinical symptom, failure of patients to present with this symptom may unduly delay the diagnosis of vitamin B_{12} deficiency and allow neurologic damage to progress without treatment. The interaction between the functions of folic acid and vitamin B_{12} has been recognized for many years and is the basis for the precautionary statement on preparations of folic acid for therapeutic use.

In the **Federal Register** of April 9, 1971 (36 FR 6843), the agency announced the conditions under which it would approve new drug applications for folic acid preparations. The labeling conditions included the following precaution: "Folic acid especially in doses above 1.0 mg daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive."

Based upon the available data and information, in the **Federal Register** of October 17, 1980 (45 FR 69043 at 69044), FDA amended the "Precautions" statement to be included

in the labeling of oral and parenteral preparations of folic acid for therapeutic use because the agency found that the revision more accurately stated the level at which folic acid may obscure pernicious anemia. The **Federal Register** notice stated that "While obscuration of pernicious anemia does not occur at levels of 0.1 mg for folate per day, hematologic remissions in pernicious anemia have been reported at levels as low as 0.25 mg of folate per day. The precautions section of the labeling conditions for folic acid preparations is amended to read as follows: 'Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations remain progressive'."

2. Food additive regulation

Folic acid is an approved food additive subject to the limitations on use set forth in the food additive regulations (§ 172.345). The food additive regulation states that: "Folic acid (folacin) may be safely added to a food for its vitamin properties, provided the maximum intake of the food as may be consumed during a period of 1 day, or as directed for use in the case of a dietary supplement, will not result in daily ingestion of the additive in excess of 0.4 mg for foods labeled without reference to age or physiologic state; and when age or the conditions of pregnancy or lactation are specified, in excess of 0.1 mg for infants, 0.3 mg for children under 4 years of age, 0.4 mg for adults and children 4 or more years of age, and 0.8 mg for pregnant or lactating women" (21 CFR 172.345). However, this regulation provides no limits, other than 0.4 mg, on the amounts that may be provided by specific foods.

In 1981, the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) reviewed evidence concerning effects of physiologic and pharmacologic doses of folic acid in patients with pernicious anemia (Ref. 5). LSRO noted that virtually all of the experimental work reviewed dealt with the administration of pteroylmonoglutamic acid (folic acid) in relatively pure forms. Responses to folic acid in food products are less well defined than responses to a pure preparation. LSRO concluded at that time that it was not possible to answer with certainty whether intakes of folic acid in foods approaching 400 μg (0.4 mg)/day could result in transient hematologic remission in patients with pernicious anemia (Ref. 5).

D. The Proposed Rule

The scientific data relating to an association between folic acid and neural tube defects that was publicly available at the time of publication of the agency's proposed rule (56 FR 60610) consisted of four clinical intervention trials in women at high risk of recurrence of these birth defects (Refs. 6 through 9), four observational studies (Refs. 10 through 13), a number of studies in which clinical parameters such as serum or red blood cell levels of folate and other vitamins were measured in women who gave birth to one or more infants with neural tube defects (Refs. 14 through 17), and studies that attempted to identify factors that may lead to neural tube defects in animal model systems (Refs. 18 through 26).

The agency developed its proposed rule on the basis of the publicly available scientific evidence. An ongoing randomized controlled trial in Hungary of multivitamin/multimineral supplementation of women at risk of an occurrence of a pregnancy complicated by a neural tube defect had been discussed at scientific meetings (Ref. 27), but the scientific data from this trial were not publicly available.

The agency proposed not to authorize the use on the labels and labeling of foods, including dietary supplements, of health claims relating to an association between ingestion of folic acid and reduction in risk of neural tube defects. The agency based its tentative decision on the available scientific evidence, which showed that daily periconceptional intake of 4 mg (4,000 μg) of folic acid was needed for reduction in risk of neural tube birth defects in women at high risk of this condition based on a previously-affected pregnancy. Among women with histories of neural tube defect-complicated pregnancies, rates for recurrence of such defects have been estimated to be as high as 2 to 10 percent compared to occurrence rates of less than 0.1 percent in the general population (Ref. 28). Thus, because of their significantly increased risk, such women have been the focus of several clinical intervention trials. The amount of folic acid found to be effective in reducing risk of recurrence was significantly in excess of usual daily intakes and exceeded the level of 0.4 mg (400 μg)/day permitted under the current food additive regulation. FDA also tentatively concluded that there was not significant scientific agreement that periconceptional supplementation with doses of folic acid lower than 4 mg (4,000μg)/day in women of childbearing age in the general U.S. population would significantly reduce the risk of occurrence of neural tube birth defects. For these reasons, FDA tentatively determined that claims on foods, including dietary supplements, relating to folic acid and reduction in risk of neural tube birth defects were not justified.

E. Recent Developments

1. New scientific data

Preliminary data from the Hungarian randomized, controlled trial of efficacy of multivitamin/multimineral supplements containing 0.8 mg (800 μg) of folic acid in preventing occurrence of neural tube defects were presented at a meeting held in May 1992 (Ref. 29). A report of preliminary results of this trial of the effects of multivitamin/multimineral supplementation in women at risk of a first occurrence of a neural tube birth defect pregnancy became publicly available in August, 1992 (Ref. 30). This trial was conducted under the auspices of the Hungarian Optimal Family Planning Program and was directed toward overall improvement in pregnancy outcomes among Hungarian women. Nonpregnant women 18 to 35 years of age without histories of infertility or previous fetal death volunteered for this program and, upon determination of eligibility, were randomized to treatment with a multivitamin/multimineral preparation containing 12 vitamins and 7 minerals or to a placebo containing 3 trace minerals only. The multivitamin/multimineral preparation contained 0.8 mg (800 μg) of folic acid. The women participated in a 3-rnonth preparation for pregnancy and began taking their assigned treatments 1 month before a planned conception. Treatments continued through the third month of pregnancy. Six cases of neural tube defects occurred in the pregnancies of 2,052 women taking the placebo, and no cases occurred in the pregnancies of 2,104 women taking the multivitamin/mineral supplement with folic acid. Based upon the preliminary results of this study, periconceptional use of a multivitamin/multimineral supplement apparently significantly reduced the rate of occurrence of isolated neural tube defects in women in the Hungarian population. However, use of the supplement did not affect the incidences of a wide range of other birth defects that occurred in both treatment groups (Ref. 30).

Results of a case-control study of periconceptional use of folic acid-containing multivitamins and risk of occurrence of neural tube defects in

women in Boston, Philadelphia, and Toronto were also presented at the meeting held in May 1992 (Ref. 29).

In the **Federal Register** of July 1, 1992 (57 FR 29323), CDC announced an open meeting in Atlanta, GA on July 27, 1992, to discuss a recommendation that all women of child-bearing age in the United States consume 0.4 mg (400 μg) of folic acid daily to reduce their risk of having a neural tube defect-complicated pregnancy. The results of the case-control study of periconceptional use of folic acid-containing multivitamins and risk of occurence of neural tube defects in women in Boston, Philadelphia, and Toronto were presented at this meeting, and the transcript of the meeting is publicly available (Ref. 31). In this study, 436 occurrent neural tube defect cases (live born and still born cases and therapeutic abortuses) were selected from metropolitan hospitals in Boston, Philadelphia, and Toronto (areas of moderate prevalence) from 1988 through 1991 and compared to 2,615 controls with other major malformations as to maternal periconceptional use of folic acid. Daily use of a folic acid-containing vitamin supplement in the periconceptional period was reported by mothers of 8 percent of cases and 13 percent of controls; the adjusted odds ratio was 0.6 (95 percent confidence interval (CI)= 0.4 to 0.8). This represented approximately a 40-percerit reduction in prevalence. A dietary folate assessment was also conducted among the mothers who did not use folic acid-containing supplements. A significant decrease in risk was found for the group who consumed 0.311 to 0.391 mg of folate daily, the adjusted odds ratio was 0.6 (95 percent CI = O.3 to 0.9). The results of this study as presented at the CDC meeting support a relationship between decreased risk of occurrent neural tube defects and periconceptional intake of either folic acid-containing multivitamins or dietary intake of folate at levels of 0.3 to 0.4 mg/day.

2. Reopening of comment period

The period for submitting comments in response to the November 27, 1991, proposal closed on February 25, 1992. In the **Federal Register** of July 23, (57 FR 32751), however, FDA reopened the comment period to permit the submission of new scientific data and information that might become available as a result of the meeting held by the CDC on July 27, 1992, and to provide an opportunity for public comment on that scientific data and information. The agency took this action, in part, because it had been advised that the scientific evidence to be discussed at the CDC meeting was not publicly available. The 1990 amendments require that the evidence relied upon by the agency as the basis for allowing health claims relating to a nutrient-disease relationship be publicly available.

3. PHS recommendation

In *Mortality and Morbidity Weekly Reports* of September 14, 1992 (Ref. 1), the Public Health Service issued a recommendation that:

> All women of childbearing age in the United States 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 with spina - bifida or other NTDs. Because the effects of high intakes are not well known, but include complicating the diagnosis of vitamin B_{12} deficiency, care should be taken to keep total folate consumption at less than 1 mg per day, except under the supervision of a physician. Women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physicians for advice.

(Ref. 1)

PHS noted that the evidence that consumption of folic acid before conception and during early pregnancy (the periconceptional period) can reduce the number of neural tube defects has been accumulating for several years and includes published data from two randomized controlled intervention trials (Refs 6, 7, and 18), two nonrandomized intervention trials (Refs 8, 9, and 33), and four observational studies (Refs. 10 through 13). Based on a synthesis of information from these studies, including those which used multivitamins containing folic acid at a daily dose level greater than 0.4 mg, it was inferred that folic acid alone at levels of 0.4 mg per day will reduce the risk of neural tube defects (Ref. 1).

In the discussion accompanying its recommendation, the PHS (Ref. 1) identified several issues that require further attention:

(1) Effective intake: The PHS (Ref. 1) recommended that all women of childbearing age should consume 0.4 mg of folic acid daily to reduce their risk of neural tube defect pregnancies The PHS (Ref. 1) noted that because supplements containing folic acid at the 0.4 mg (400 μg) level are widely available, this dosage has been the focus of the available observational research studies. PHS also noted that "it is possible that lower doses of folic acid may reduce the risk of neural tube defects, but further research would be needed to learn the minimum effective dose" (Ref. 1).

(2) Multivitamins: The PHS recommendation for the use of folic acid alone was, by necessity, derived by inference from results of the available studies. The Medical Research Council intervention trial included a group of women who used folic acid at a dose of 4 mg per day (plus calcium and iron) and who could be compared with a control group taking calcium and iron only (Ref. 6). Thus, the specificity of folic acid as an etiologic agent in reducing recurrences by 72 percent was established for the study population at this high dose. In contrast, all four observational studies and two of the other three intervention trials measured the use of folic acid-containing multivitamins. Folic acid content and content of other nutrients in these preparations varied, or in some cases, could not be identified (Ref. 1). The preparations used in studies that obtained this information contained (at least) vitamin A, vitamin D, thiamin, riboflavin, pyridoxine, vitamin C, and niacin in addition to folic acid.

Thus, the possibility that nutrients other than folic acid, particularly at intakes of folic acid less than 4 mg daily, could contribute to the protective effect warrants further discussion.

(3) "Folate-preventable" fraction of neural tube defects in the U.S. population: The PHS recommendation recognized that protective effects against occurrence of neural tube defects found in observational studies of multivitamins containing low doses of folic acid have ranged from none to substantial (Ref 1) Based on the information available, the PHS suggested that a reasonable estimate of the expected reduction in neural tube defects in women in the general U.S. population was 50 percent (Ref 1).

This issue warrants further discussion because estimates of the magnitude of the preventable fraction and the variation in risks among subgroups of women of child-bearing age may affect decisions as to the best method of implementation.

(4) Safety confederations. The PHS recommendation advised women that care should be taken that folate consumption not exceed 1 mg (1,000 μg)/day except under the supervision of a physician because the effects of higher intakes are not well known (Ref 1). One of the adverse effects noted was the effect of high intakes on the making a diagnosis of vitamin B_{12} deficiency

The agency recognizes the risk that increased intakes of folic acid will complicate the diagnoses of the anemia of vitamin B_{12} deficiency and thereby allow the neurological damage caused by this vitamin deficiency to progress

untreated. Several other safety considerations are identified below. These issues also warrant further discussion as the questions of whether and how to provide for a health claim are evaluated.

II. Comments on the Proposed Rule

A. Introduction

The agency received approximately 150 comments in response to its proposed decision on health claims for folic acid and neural tube defects. Comments were received from: Consumers, consumer advocacy groups, national professional organizations of nutrition educators, national professional organizations of dietitians, organizations of Federal, state, and local regulatory officials, state and territorial public health nutrition directors, manufacturers and suppliers of vitamins to the conventional food industry and dietary supplement industry, trade associations of nutritional supplement manufacturers, practicing physicians and dietitians, and a foreign government. A number of comments were received that were more appropriately answered in other dockets, and these were forwarded to the appropriate docket for response.

FDA has considered all of the comments on folic acid and neural tube defects that it received. The agency reviewed all of the documents, including letters, press releases, scientific articles and data supporting those articles, review articles, and recommendations that were included in the comments. A summary of the comments that the agency received and the agency's responses follow:

B. Comments

1 Several comments suggested that health claims should be allowed if potential benefits exceed risks, and that FDA should have used a risk/benefit analysis in determining the validity of health claims. Other comments stated that supplementation with folic acid is essentially risk-free.

FDA disagrees with this comment Section 403(r)(3)(B)(i) of the act requires that a decision to authorize a health claim be based on the totality of the publicly available scientific evidence and on significant agreement among experts qualified by training and experience to evaluate such evidence that the evidence supports a claim The concept of "no risk" as a justification for a health claim is inconsistent with the requirements of the 1990 amendments. Moreover, there are safety concerns associated with increased intakes of folic acid. These concerns are discussed below.

2. Several comments asked whether studies must be carried out in the United States for health claims. These comments noted that for the calcium/osteoporosis claim, much of the data related to peek bone mass was derived from studies in rural Yugoslavia and found lo be "generalizable" to the U.S. population, but for folic acid and neural tube defects, data from non-U.S. populations studies seemed not to be acceptable to FDA. The comment also stated that in rejecting the folic acid/neural tube defect claim, FDA relied heavily on the argument that much of the data was from non-U.S. studies.

In the proposed rule on general requirements for health claims (56 FR 60610 at 60549), FDA stated that consistent results from different types of well-conducted human studies, by different investigators, in different populations would contribute to the totality of scientific evidence from which a valid health claim may be developed. In its November 27, 1991 proposal on folic acid and neural tube defects (56 FR 60610), FDA stated that it was unable to directly apply results from some studies done outside of the United States because these studies were conducted on populations at significantly higher risk than the U.S. population, they lacked adequate control groups, or they were multiply confounded.

FDA participated in the development of the recently published PHS recommendation (Ref. 1). This recommendation relied heavily upon data from other countries and was developed by combining the results from several types of studies carried out in the United Kingdom, Hungary, Cuba, Western Australia, and the United States. Thus, the folic acid rulemaking does not evidence an unwillingness on the part of FDA to consider studies on non-U.S. populations. However, the characteristics of the population at issue may affect the relevance of the study to the FDA's rulemaking.

3. Comments received from state and national professional organizations, an organization of Federal, state, and local regulatory officials, and U.S. state attorneys general were supportive of FDA's proposed rule denying a health claim for folic acid and neural tube defects. One comment stated that the preponderance of scientific literature does not strongly support such a relationship. Another comment recommended that statements regarding the relationship between folic acid and neural tube defects be postponed until further studies have been completed. One comment stated that when the confounding variables relating to the causation of neural tube defects are also considered, the wholesale claim that folic acid supplementation will reduce neural tube defects becomes even more unfounded. Another comment cited the irreversible neurological damage that can result from excess intake of folic acid by persons with undiagnosed pernicious anemia and noted that maternal hyperthermia (for example, from use of hot tubs during the first month following conception) was a recognized risk factor for neural tube defects.

Several comments stated that FDA should allow a health claim that "Folic acid intakes, at about the U.S. RDA level of 400 μg/day, have been associated with significantly lowered risk of severe birth defects, including spina bifida." A consumer advocacy group recommended that a claim for folic acid and neural tube defects be permitted only on supplements containing free folic acid because there is evidence that neural tube defects will be reduced by such supplements. The comment noted further that there is additional evidence that the incidence of neural tube defects may be reduced by food sources of folate, although there is currently no consensus on this point.

These comments raise several important issues. The agency agrees that neural tube defects are multifactorial in nature. A history of neural tube defects is the single greatest risk factor currently recognized. However, the well-conducted Medical Research Council trial (Ref. 6) demonstrated a specific relationship between intake of high doses of folic acid and reduction in risk of recurrence of some neural tube defects in women at increased risk of this complication because of a prior affected pregnancy. The effect of lower doses of folic acid on neural tube defects is less clear. However, based upon a synthesis of information from several studies (including a major study that became available after FDA published its proposal in November, 1991) (Ref .31), all of which recorded use of multivitamins containing varying levels of folic acid, PHS has recommended that all women of childbearing age consume 0.4 mg (400 μg) of folic acid per day for the purpose of reducing their risk of neural tube defect-complicated pregnancy (Ref. 1).

With regard to the issue of effectiveness of nonsupplement food sources of folate in reducing the incidence of neural tube defects, the agency notes that the vast majority of women do not experience an occurrence of a pregnancy complicated by a neural

tube defect, and the available evidence does not provide clear evidence of the optimum folate intake to prevent this complication. Although the lowest effective dose is not known, the PHS concluded that 0.4 mg (400 μg)/day is an effective dose. Dietary folate insufficiency per se does not seem to be causative in neural tube defects. The vast majority of women appear not to be predisposed to have a folate-related neural tube defect pregnancy. Data from the observational study of Milunsky et al., 1989 (Ref. 13) suggested that women whose diets contained more than 100 μg of folic acid had a lower risk of a neural tube defect pregnancy than did women whose diets contained less than 100 μg folate per day. Laurence (1983) (Ref. 32) observed that when dietary counseling to improve overall diets was provided to women at risk of a recurrence of a neural tube defect, and when such improved diets were consumed, risk reduction approached 50 percent. Similarly, a case-control study conducted in Western Australia suggested that diets containing increased amounts of folic acid, vitamin C, beta-carotene, and fiber (nutrients associated with fruits and vegetables), were protective against occurrence of neural tube defects (Ref. 11). Therefore, the agency believes, that with respect to options for implementation, the scientific data provide a basis for further discussion of the appropriate intake and source.

4. Several comments stated that FDA, in developing its proposed rule regarding folic acid and neural tube-defects, rejected conclusions of the LSRO report (Ref. 33). Several comments, quoted from conclusions of the LSRO report to support a health claim and stated that the conclusions of the LSRO report contributed to the significant scientific agreement that existed regarding the validity of a health claim respecting folio acid and neural tube defects.

The agency contracted with the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (LSRO/FASEB; FDA Contract No. 223-88-2124, Task Order No. 9) to independently evaluate the scientific literature respecting folic acid and neural tube defects. At the time of publication of FDA's proposal in November, 1991, FDA had available a draft copy of the LSRO report "Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships: 1. Folic Acid and Neural Tube Defects" (Ref. 33). In its proposal (56 FR 60610), FDA noted several concerns with the LSRO report, including its failure to focus on the specific relationship of folic acid to neural tube defects in studies where multiple nutrients were given, or where specific nutrient effects could not be isolated; its failure to differentiate between risk of occurrence and risk of recurrence of neural tube defects; and its failure to differentiate between daily doses of 4 mg (4,000 μg) versus 400 μg in terms of effectiveness in reducing the risk of neural tube defects.

LSRO/FASEB submitted its final report as a comment in February 1992 (Ref. 34). The agency's concerns with the draft report were not addressed in the final LSRO report. Therefore, because the final LSRO/FASEB report did not differ from the draft report available to the agency before publication of its proposal, no change in FDA/s tentative conclusion is Warranted.

The agency notes, however, that there are significant areas in which the agency's proposed rule and the LSRO/FASEB report (Refs. 33 and 34) are in Agreement. For example, the agency is in agreement with the report on the following topics; (1) That 4 mg of folic acid has been demonstrated to have a protective effect against development of neural tube defects, (2) that there is no evidence that the effect of folic acid is long-lasting as a protectant or potential - protectant against neural tube defects, (3) that in addition to maternal and fetal nutrition, other individual, dietary, nutrition, and health factors also contribute to the risk of neural tube defects, (4) that there are significant gaps in our knowledge of the etiology of neural tube defects and of how folic acid either alone or in conjunction with other vitamins may protect against. neural tube defects, and (5) that it is currently unknown whether neural tube defects are caused by a gene-dependent or drug-induced vitamin dependency requiring a higher than physiological intake of folic acid or other micronutrient.

5. Several comments stated that following publication of the results of the Medical Research Council's trial in July 1991 (Ref. 6), significant scientific agreement emerged concerning the importance of folic acid for the prevention of neural tube birth defects.

FDA agrees that the Medical Research Council's randomized double-blind multicenter trial (Ref. 6) clearly found a significant reduction in recurrence rate of neural tube defects in women supplemented periconceptionally with 4 mg folic acid/day. No protective effects of vitamins other than folic acid were observed. The Medical Research Council's study established a specific role for folic acid in reduction in risk of recurrence in a significant proportion of women at high risk of this complication because of a history of neural tube defect pregnancies. This study did not investigate the efficacy of doses of folic acid lower than 4 mg (4,000 μg) per day. Based on a synthesis of available studies, however, including preliminary results of the Hungarian intervention trial, the PHS has inferred that a lower intake of folic acid will reduce the risk of occurrence of neural tube defects. However, a number of concerns have arisen with respect to the effects of a folic acid health claim that must be resolved before such a claim can be authorized.

6. A number of comments identified options for implementing a health claim, suggested means by which the folate status of the population can be improved, recommended daily closes of folic acid lower than 400 μg, identified safety concerns, or expressed concerns about the current food additive regulation on folic acid. Because these comments largely address the issues raised as needing resolution in the discussion accompanying the PHS recommendation (Ref. 1), FDA believes that it is useful to summarize these comments. However, given the ongoing nature of this rulemaking process, responses to these comments are not possible now but are likely to emerge as the process proceeds.

1. Proposed criteria for health claims and use of the food additive regulation

Several comments stated that the agency should establish criteria for foods or supplements making folic add claims and proposed such criteria. For example, a comment suggested that requiring foods and supplements to contain more than 20 percent of the reference daily intake would be inappropriate because the widespread fortification of foods might lead to excessive folacin intakes. The comment further suggested that the agency monitor folacin intakes closely after health claims for folic acid appear in the marketplace to determine whether the public is ingesting levels that greatly exceed or fall short of the recommended daily intake of 400 μg. The comment recommended that if the agency found that excess intakes of folic acid posed a risk, it could restrict either the number of foods or supplements to which the vitamin could be added or the maximum levels allowed in foods or supplements, according to the food additive regulation for folic acid. Alternatively, the comment suggested that FDA could lower the minimum folic acid content of foods or

supplements that are allowed to make health claims.

FDA intends to review the question of the appropriate level of folic acid in food. However, the agency notes that the nature of the rulemaking process, particularly the formal rulemaking process applicable to food additives, does not provide the flexibility or responsiveness envisioned by the comment.

Another comment stated that the agency should require full and nondeceptive health claims concerning neural tube defects and folic acid so that consumers are not misled into believing that folic acid might prevent all neural tube defects or reduce the risk of nonneural tube defect birth defects. The comment emphasized that the agency should ensure that claims on folic acid-containing supplements provide full and nondeceptive information. The comment stated that a nondeceptive claim would state that: (a) Folic acid reduces the risk of only neural tube birth defects; (b) scientists estimate that folic acid intakes may prevent only half of neural tube defects; (c) consuming more than 400 μg (0.4 mg) of folic acid daily will not necessarily provide additional protection against birth defects; and (d) scientists have not fully evaluated the safety of doses higher than 800 μg (0.8 mg).

The act requires mat claims on foods must be truthful and not misleading. The failure to disclose material facts would render a claim misleading under section 403(a) of the act. The agency agrees that, based on the results of the Medical Research Council trial (Ref. 6), the association between folic acid intake and birth defects is specifically related to neural tube defects. This trial also found that folic acid, while significantly reducing the risk of neural tube defects in women at high risk of recurrence of this complication, did not significantly alter the incidences of a wide variety of other birth defects in the population studied. Therefore, in deciding whether to authorize a health claim, the agency will consider whether such a claim should specifically state that the only types of birth defects for which an association with folic acid has been identified are neural tube defects, such as anencephaly, spina bifida, and anencephalocoele.

2. Effective intake

One comment stated that better information on the lowest effective level of folic acid is desirable in order to provide as strong a basis as possible for a food fortification program. Another comment noted that the available data suggest that the recommended level of 400 μg of folic acid/day is probably considerably higher than is actually needed to achieve protection. Several comments suggested that a daily dose of 0.2 mg folate (200 μg) was probably adequate for reduction in risk of neural tube defects, and that data from older as well as more recent studies support such a conclusion. Several comments stated that the consideration of efficacy of lower doses is important because there are uncertainties as to whether daily supplements of folic acid plus iron can reduce zinc absorption and result in intrauterine growth retardation in pregnant women.

The question of effective intake was highlighted by PHS. This issue was addressed by the advisory committee that FDA convened. Although PHS acknowledged that there may be a lower dose that is effective, it concluded that all women who could become pregnant should ingest 0.4 mg of folic acid daily to reduce their risk of having a pregnancy affected with a neural tube defect (Ref.1).

3. Specific safety issues

Another comment observed that widespread fortification of the food supply could result from authorization of a health claim as products added folate in order to claim that they were useful in reducing the risk of neural tube defects. The comment noted that following such fortification, the usual intake of folic acid by the U.S. population would rise from about 250 μg/day/person to about 3 to 4 mg (3,000 to 4,000 μg/day/person, and that the safety of such an outcome is by no means clear. The comment identified large segments of the population with low vitamin B_{12} status and mentioned the potential for development of neurological deficits in such persons as a result of a food supply highly fortified with folic acid. The comment urged the agency to delay action until a full public airing permits a review of all of the implications of each approach to policy in this and related areas. One comment stated that the proposed intake of 0.4 mg (400 μg) should be evaluated in subjects with low zinc status because findings from the United States, Sweden, and Britain suggest that low zinc status is much more common in pregnancy than has been previously suspected, and that zinc deficiency is a known cause of neural tube defects in animal model systems. The comment cited several references that reported that folate can interfere with the utilization of dietary zinc.

These issues were considered by the advisory committee that FDA convened and by the agency in reaching a final decision in this matter.

4. Options for implementation

One comment noted that while the quickest and easiest approach to increasing the folate intake of women of reproductive age is to encourage the consumption of folic acid supplements, compliance with such a program would be poor. The comment noted that many adolescent women refuse to use birth control even when provided free of charge and choose not to protect themselves against life-threatening diseases, such as acquired immunodeficiency syndrome (AIDS). Several comments observed that because of the higher rates of neural tube defects among women from lower socioeconomic status groups, alternatives to a "one-a-day" pill method of implementation should be considered. Several comments recommended that fortification of a staple food would likely reach greater numbers of women than would programs utilizing the pill approach. One comment stated that food fortification would require careful documentation of population distributions of consumption of the designated foodstuffs by age, gender, and socioeconomic status. Several comments also included references dealing with the folate status of specific subgroups of the U.S. population and suggested that fortification of staple foods in the food supply would be an appropriate method of improving folate status. The comment noted groups within the population identified in surveys or in clinical studies as at potential risk of folate deficiency include children, adolescents, adults (including pregnant women), and the elderly who could also benefit from folate fortification. Comments also identified other segments of the population at risk of low folate status as those who use alcohol, oral contraceptives, antifolates, and specific nonsteroidal, anti-inflammatory drugs.

Again, the comments parallel concerns that were raised by PHS. They will be fully addressed by the agency in deciding, if a health claim is authorized, what is the most effective method of presenting the claim to the U.S. public.

III. Review of the Recent Scientific Literature

In addition to its evaluation of all comments received in response to its proposed rule regarding folic acid and neural tube defects, FDA, using the same criteria identified in the proposal (56 FR 60610 at 60614), also reviewed the scientific literature, including

human studies and studies in animal model systems, that has become publicly available since publication of its proposed rule relative to the relationship between folic acid and neural tube defects.

A. Human Studies

1. Laurence (1991) (Ref. 35) reported the results of an uncontrolled folic acid supplementation trial in women who had a previous pregnancy complicated by a neural tube defect. Women in Cardiff, United Kingdom, at recurrent risk of a neural tube defect pregnancy and who declined to participate in the Medical Research Council trial (Ref. 6) were advised to take a supplement containing 4 mg folic acid and minerals for not less than 1 month before conception and continuing until 12 weeks of gestation. Laurence (1991) (Ref. 35) reported that there were two (2) recurrences of neural tube defects among 234 pregnancies (recurrence risk of 8.5 per 1,000) in the supplemented women. The estimated risk for recurrence among untreated women (none were included in the trial) was about 30 per 1,000. Laurence (1991) (Ref. 35) estimated that the folic acid plus minerals supplementation reduced the risk of recurrence of neural tube defects by more than two-thirds. The author noted that although this was an uncontrolled trial, folic acid should be offered to all high risk women planning further pregnancies.

2. Measurement of maternal or fetal blood levels of specific vitamins is one method used to test the hypothesis that folic acid status is directly related to risk of neural tube defects. Several investigations have tested this hypothesis by determining whether occurrence of neural tube defects is associated with decreased maternal levels of vitamins (Refs. 14 through 17). A recently reported study , Holzgreve et al. (1991) (Ref. 36), found no differences in serum, and erythrocyte folate in blood samples from fetuses with neural tube defects (n=17) or fetuses without such defects (n=45). Samples were obtained at 16 to 22 weeks of gestational age. The folate level of women pregnant with a neural tube defect-affected fetus was normal, and nutritional status did not differ between the two groups. The authors rioted that their findings of no correlation between neural tube defects and fetal blood folate values do not necessarily contradict the Medical Research Council study (Ret. 6) but show that an easy explanation for the protective effect of folate observed in the British study cannot as yet be provided. The authors also stated that further research is needed to define the role of micronutrients in the development of neural tube defects.

3. The results of the Medical Research Council trial (Ref. 15) demonstrated that women at very high risk of having a recurrence of a neural tube defect-complicated pregnancy could significantly reduce their risk by taking a high level of folic acid periconceptionally. Other investigators have attempted to determine how these results might apply to a general population of women at much lower risk of occurrence of neural tube defects. Mills et al. (1992) (Ref. 37) measured levels of folate, vitamin B_{12} and retinol in maternal serum samples drawn early in 89 pregnancies resulting in neural tube defect offspring and in 178 control pregnancies. Samples were obtained within 8 weeks of neural tube closure. The results of this population-based study in Finland, a low prevalence area for neural tube defects, demonstrated no relationship between maternal serum folate, vitamin B_{12}, and retinol during pregnancy and the risk of neural tube defects.

B. Animal Studies

Studies with animal model systems are one of several lines of evidence that are used to establish associations between various nutrients or toxicants and birth defects. The relationship between folate deficiency and the incidence of neural tube defects in experimental animal model systems is not clear. A variety of protocols have been used to study the relationship between nutritional status and risk of neural tube defects (56 FR 60610). The anticonvulsant drug valproic acid is suspected of causing neural tube defects in humans. The mechanism for such effects is unknown but has been postulated to involve induction of a deficiency of folic acid. Hansen and Grafton (1991) (Ref. 38) examined this possibility by culturing rat embryos concurrently in valproic acid and folinic acid, a folic acid derivative. The authors reported a dose-related increase in the number of open neural tubes in rat embryos cultured in valproic acid. When various concentrations of folinic acid were added in combination with a teratogenic dose of valproic acid, there was no decrease in the incidence of open neural tubes. The results of this study suggested that valproic acid-induced open neural tubes in this experimental animal model system are not the result of a deficiency of folic acid.

However, Wegner and Nau (1991) (Ref. 39) also studied the protective effects of folinic acid against valproic acid-induced neural tube defects in the mouse and reported a different result. These authors observed significant diurnal variations in folate metabolism in mouse embryos between days 8.5 and 9.5 of gestation. They measured significant time dependent protective effects against valproic acid-induced teratogenesis such that folinic acid reduced neural tube defects when provided at one time period but not when provided at another time period. Such findings indicate the extreme sensitivity of developing embryonic (issue to external factors and are of importance in considering interactions of drugs with folate metabolism as a possible mechanism of teratogenesis (Ref. 39).

Other investigations have sought to determine whether mice deficient only in folic acid produce embryos with neural tube defects. For example, Heid et al, 1992 (Ret. 40) used folate-free amino acid-based diets for producing well-defined dietary concentrations of folic acid for rats and mice. Heid et al (Ref. 40) reported that when Swiss-Webster mice were fed inadequate dietary folic acid, fewer and smaller embryos (that developed normally) were produced during pregnancy. Their studies indicated that folate deficiency alone is insufficient to produce neural tube defects in Swiss-Webster mice.

C. Authoritative Statements

1. Institute of Medicine, National Academy of Sciences

In 1990, the Institute of Medicine of the National Academy of Sciences published its report, "Nutrition During Pregnancy" (Ref. 28). The Institute of Medicine updated this report in 1992 (Refs. 41 and 42) to reflect new data (primarily the results of the Medical Research Council trial; Ref. 6) that had become available since the first publication of the report. Data from the Hungarian randomized intervention trial were not publicly available at the time the report, was updated. The report noted that a previous history of a neural tube defect should alert health care providers to the need for preventive measures before a subsequent pregnancy. The report recommended that women with a history of neural tube defect-complicated pregnancy follow the CDC recommendations (Refs. 41 and 42) for high-dose folic acid supplementation (preconceptionally and throughout the first trimester, under a physician's supervision) to reduce their risk of recurrent neural tube defects (Refs. 41 and 42). The report noted that questions remain concerning the etiology of neural tube defects, the most appropriate dosage, and the

appropriate role of nutrition in preventing first occurrences.

2. World Health Organization

That there is still considerable uncertainty as to how best to reduce the risk of neural tube defects is shown by information in a recently published "World Health Organization (WHO) Drug Information Bulletin" (Ref. 43). The bulletin notes that an expert advisory committee has now been set up in the United Kingdom to consider how best to ensure that all women likely to become pregnant receive supplementary folic acid (Ref. 44). The WHO Bulletin states "Unfortunately the available data provide no indication of how long supplementation needs to be continued to obtain the maximum effect, or of whether the same protective effect can be obtained with lower doses. These are matters of some importance because it may be impracticable to supply a supplement of 4 mg daily from dietary sources alone. Some empiricism will be required to arrive at a recommendation. Short of conducting a further trial with different dosage regimens, formal demonstration of a dose-effect relationship will remain outstanding" (Ref. 43). FDA notes that data from the Hungarian intervention trial were not publicly available at the time this statement was prepared.

D. Conclusions from the Recent Scientific Literature

The recent scientific literature, including studies in humans and animals, is consistent with PHS recommendation
issues that PHS noted as needing resolution.

IV. Actions on Folic Acid

A. Determination That No Claim Can be Authorized at This Time

Section 403(r)(3)(B)(i) of the act states that FDA is to grant a health claim when there is significant scientific agreement that the scientific data relating a nutrient to a disease of health condition supports such a claim. The recent PHS recommendation (Ref. 1) evidences that such agreement exists. However, the Food, Drug and Cosmetic Act must be read as a whole.

Sections 403(r)(3)(A)(ii), 402(a), and 409 of the act express the proposition that the use of a substance in food must be safe. As the PHS recommendation states (Ref. 1), there are significant questions that persist about the use of folic acid in food. Questions raised in the PHS recommendation (see section I.E.3. of this document) include the Safety of high intakes by both the target population as well as by other segments of the population who may unintentionally be exposed to high intakes if overfortification of the food supply were to occur as a result of the PHS recommendation. There are, additionally, several other unresolved scientific questions that will require discussion before a claim is authorized.

Based on these concerns, FDA concludes that under section 403(r)(3) of the act, it cannot authorize a health claim on folic acid and neural tube defects. FDA is concerned that the possibility exists that folic acid itself could be a substance that increases the risk of a disease or a health-related condition in persons in the general population (see section 403(r)(3)(A)(ii) of the act). Therefore, FDA concludes that it cannot authorize a health claim on folic acid until the questions regarding the safety of the use of this nutrient as well as the other concerns raised by PHS are satisfactorily resolved. However, the agency is undertaking efforts to address and resolve these concerns. The remainder of this document outlines how the agency will do so.

B. Issues

1. Estimation of range of increased intakes

FDA expects that there would likely be a significant increase in consumption of folic acid by women in their childbearing years, and by the general population, if a health claim were to be authorized because manufacturers would add folic acid to their products in order to claim that these products are useful in reducing the risk of birth defects. Intakes of multiple doses of free folic acid in the form of supplements and from its increased presence in the food supply could rapidly result in intakes of more than 3 mg (3,000 μg)/day by persons in the target population as well as by persons in the general population (see Table, Estimate A). Considerably higher amounts of folic acid (approximately 7 mg (7,000 μg}/day) could be consumed by subgroups of the population (e.g., teen-age and young adult males, heavy users of supplements) (see Table, Estimate B).

a. *Differences in bioavailability between free folic acid and food folates.* It is well-recognized that the bioavailability of free folic acid (the form included in dietary supplements and in fortified foods) is several-fold greater than that of naturally occurring food folates. Estimates of the increased bioavailability ("potency") of free folic acid relative to food folates range from at least 2-fold to 4-fold or greater (Ref. 45). The pronounced differences in bioavailability between free folic acid and food folates must be factored into considerations of appropriate dose as well as considerations of potential safety issues.

b. *History of use.* Because the National Research Council recommended daily allowances have been set below 500 μg of food folates ("folacin") (except those for pregnant women) since 1968 (Refs. 46, 47, and 48), and because the food additive regulation has limited the amount of free folic acid added to fortified foods and supplements to 400 μg/day (except Supplements for pregnant or lactating women), there is no history of long-term use by persons in the general U.S. population, including pregnant women, of dally intakes of free folic acid in excess of about 1 mg (1,000 μg). Therefore, potential safety concerns must be addressed.

2. Specific safety issues and estimates of magnitude

If a wide variety of food sources were fortified with 400 μg folic acid/serving, as would likely occur following authorization of a health claim, intakes of folic acid could easily reach 3 mg (3,000μg)/day or higher. FDA's concerns regarding large increases in folic acid fortification, and the large increases in intake that would result, are summarized below.

a. *Vitamin B_{12}*–related issues. (i) Issue: As mentioned above, in the presence of excess folic acid and inadequate vitamin B_{12}, the anemia of vitamin B_{12} deficiency may not develop but severe and irreversible nerve damage may continue. This interaction between the functions of folic acid and vitamin B_{12} has been recognized for many years and is the basis for the precautionary statement on oral and parenteral preparations of folic acid for therapeutic use in treating folate-deficiency anemias. The agency is reviewing the literature upon which this concern is based.

In 1945, folic acid was introduced as a possibly specific substance for the treatment of pernicious anemia. A large number of reports based on small numbers of cases studied for short periods of time followed the introduction of this new therapy (Ref. 49). It was soon recognized that the two manifestations of pernicious anemia (the hematologic disturbances and the neurologic disturbances) responded differently to therapy with folic acid. Reports began to appear in the literature calling attention to the deleterious and sometimes "explosively" harmful effects of folic acid on the neurologic

manifestations of the disease (Refs. 50 through 53).

There is ample evidence that most patients with pernicious anemia respond hematologically to folic acid (Refs. 54 through 59). Doses of 1 to 5 mg folic acid can reverse the hematologic abnormalities of the deficiency (Refs. 60 through 64). Hematologic improvement in pernicious anemia has also been noted at doses of folic acid lower than 1 mg (e.g., 200 to 500 μg) (Refs. 58, 59, 65 through 67, and 100), but the responses have been less predictable than those to doses of 1 to 5 mg. For example, Chosy et al. (1962) (Ref. 66) reported that daily injections of 400 μg of folic acid caused hematologic responses in some patients with pernicious anemia. Some investigators have not been convinced that amounts of folic acid within the range of 200 to 500 μg/day would mask pernicious anemia (Refs. 65, 68, and 101), while others have reported suboptimal responses to 500 μg of folic acid in patients with pernicious anemia (Refs. 58 and 59).

On the basis of the degree of reticulocyte response, 200 μg folic acid has been used to differentiate between the megaloblastic anemias caused by folate deficiency and vitamin B_{12} deficiency (Ref. 69). Chanarin (1969) (Ref. 69) cautioned that this use should not be interpreted to mean that long-term administration of 200 μg of folic acid could not mask pernicious anemia in some otherwise untreated patients. Herbert (1975) (Ref. 70) and Herbert, et al. (1980) (Ref. 71) recommended that 100 μg folic acid be administered orally in therapeutic trials. This dosage has been shown to provide a maximal hematologic response in patients with folate deficiency but not in those with vitamin B_{12} deficiency (Ref. 72). This finding is in agreement with the statement of Chanarin (1969) (Ref. 69) that doses of folic acid greater than 200 μg/day might produce hematologic responses in some patients with pernicious anemia.

Pernicious anemia is not an insignificant or rare condition in the United States (see section IV.B.2.a.ii of this document), nor is its diagnosis always straightforward. For example, Lindenbaum et al. (1990) (Ref. 73) has reported that while serum cobalamin levels have been generally considered to be essentially 100 percent sensitive in the detection of clinical disorders caused by cobalamin deficiency, there is a significant minority of patients with cobalamin deficiency whose serum cobalamin levels are normal. In such individuals, measurements of serum metabolite concentrations of methylmalonic acid and total homocysteine may be necessary to facilitate the diagnosis of vitamin B_{12} deficiency (Ref. 73).

In summary, the available evidence indicates that some patients with pernicious anemia will respond to folate therapy in doses less than 500 μg/day. Other individuals with pernicious anemia will not exhibit hematologic remission at such doses but will respond to doses of 1 mg of folic acid and higher. It is not possible to answer with certainty whether intakes of folic acid in foods approaching 400 μg/day could result in transient hematologic remission in patients with pernicious. anemia. The agency believes that this issue warrants further discussion.

(ii) Estimates of magnitude: Vitamin B_{12} deficiency anemias are not uncommon in the U.S. population. Information from the National Center for Health Statistics indicates that there were 740,000 patient visits to physicians' offices with a diagnosis of pernicious anemia during the 2-year interval 1989 to 1990 (Ref. 74). Approximately 524,000 of these visits were by women (Ref. 74). An additional 16,000 patient visits during this interval involved a diagnosis of other vitamin B_{12} deficiencies (for example, those associated with consumption of vegetarian diets).

National Center for Health Statistics records from the National Hospital Discharge survey for 1990 identified 31,000 discharges that included a diagnosis of pernicious anemia and an additional 7,000 discharges that included a diagnosis of other vitamin B_{12} deficiency anemia (Ref. 75).

It is recognized that among African-Americans, particularly African-American women, pernicious anemia is not confined to the elderly, as it generally is among whites (Refs. 76 through 78). Thus, a large subgroup of young African-American women in the general population may be especially vulnerable to adverse effects of significantly increased intakes of folic acid.

Although the number of "visits" recorded in the ambulatory care surveys mentioned above include multiple visits by some patients, the data show that pernicious anemia is not an insignificant or rare condition in the U.S. population. There is currently no way to determine how many persons in the general U.S. population have undiagnosed vitamin B_{12} deficiency. A large number of people have subnormal levels of serum vitamin B_{12} without having any classical manifestations of vitamin B_{12} deficiency (Refs. 79 and 80). Ten to twenty percent of elderly persons, more than 25 percent of demented patients, 15 to 20 percent of AIDS patients, and 15 to 20 percent of patients with malignant diseases have low serum vitamin B_{12} levels. In addition, 5 to 10 percent of all patients, regardless of age or clinical status, are found to have low serum B_{12} levels. Metabolic and subtle neurologic dysfunction are demonstrable in a significant fraction of such cases (Ref. 79). Very little is known about whether folate supplementation has any effect on such persons, who are more numerous in the population than are patients with pernicious anemia (Ref. 79). This issue requires consideration in assessing the potential impact of increased intakes of folic acid.

b. *Risks to pregnant women*. In "Nutrition During Pregnancy," the Institute of Medicine (IOM) stated that the safety of large doses of folic acid during pregnancy has not been systematically determined (Ref. 28). The IOM noted that large doses of folic acid may inhibit the absorption of other nutrients by competitive interaction and can also obscure the diagnosis of onset or relapse of pernicious anemia which is extremely rare in women of childbearing age. The IOM recommended modest supplementation for some segments of the U.S. population at risk of folate inadequacy. Such subpopulations include some pregnant women who lack the knowledge or financial resources to purchase adequate food, abusers of alcohol, cigarettes, or drugs, those with malabsorption syndromes, pregnant adolescents, and women bearing more than one fetus. Based upon data available at the time, the IOM recommended 300μg folate daily during pregnancy for such subpopulations (Ref. 28).

(i) Issue. A potential risk of increased folic acid supplementation involves effects of high blood levels of free folic acid on the embryo during early gestation. The Medical Research Council study that treated women at high risk of a recurrence of a neural tube defect pregnancy with 4 mg folic acid daily did not have the power to ascertain the safety of such high level supplementation in the population studied. This concern was stated by the study's author (Ref. 6). The agency noted above that there is no history of long-term use in the United States of folic acid at levels at or above about 1 mg/day.

(ii) Estimate of magnitude. About 4 million pregnancies occur in the United States each year. The concern regarding the lack of safety data for high doses of 1 folic acid in pregnant women has been

discussed in the scientific literature since the report of the successful Medical Research Council trial (Ref. 6). For example, Leeming et al. (1991) (Ref. 81) stated that while 4 mg of folic acid until 12 weeks of pregnancy may reduce the incidence of neural tube defects in women at high risk of recurrence, there may also be damaging effects. These authors suggested that substantial amounts of unmetabolized folic acid appear in the plasma after a single high dose and suggested that high circulating levels of folic acid may damage developing neural tissue during early embryonic development. They further noted that high levels of folic acid are not normally found in the circulation. Scott et al. (1991) (Ref. 82) also suggested the seriousness of risk during early embryonic development. They stated that while the fully developed brain may be protected from neurotoxic effects of high circulating levels of folic acid, no information is available as to whether developing neural tissue is similarly protected.

c. *Persons with epilepsy* (i) Issue. The possibility has been raised that folic acid supplements in high doses may reverse the effectiveness of anticonvulsant medication (Ref. 83). Folic acid and certain anticonvulsants compete with each other for receptors on brain cells. A potential concern is whether high intakes of folic acid exacerbate seizures in persons with uncontrolled or with drug-controlled epilepsy.

(ii) Estimates of magnitude. There are an estimated 200,000 persons in the United States whose epilepsy is not controlled. Most studies on the effects of folic acid in persons with drug controlled epilepsy have involved institutionalized individuals and responses to increased intakes have been variable.

d. *Persons taking drugs that interfere with folate metabolism*. (i) Issue. Folate antagonists such as Methotrexate are used in the treatment of various cancers, including leukemias (Ref. 84). In addition, low doses of Methotrexate are currently used in the treatment of psoriasis, rheumatoid arthritis, and bronchial asthma. The antifolate Trimethoprim is used to treat bacterial infections. Other therapeutic drugs that interfere with folate metabolism include: Pyrimethamine, Triamterene, sulfasalazine, colchicines, phenyltoin, and Trimetrexate (Ref. 84). Recognition of the therapeutic usefulness of these antifolate drugs for the conditions above has developed during the last 30 years.

(ii) Estimates of magnitude. The drugs mentioned above are used in the treatment of: Psoriasis, rheumatoid arthritis, bronchial asthma, malaria, hypertension, Crohn's disease, gout, epilepsy, and AIDS. Taken together, many of these conditions effect significant portions of the general U.S. population.

The safety of significantly increased folate intakes by persons with these disorders, whether or not they are receiving antifolate medications, remains an open question (Ref. 85). The safety or toxicity of oral folic acid supplements in persons who are being treated with drugs known to interfere with folate metabolism requires further discussion.

It is not known whether substantially increased intakes of folic acid would impair (or reverse) the therapeutic effectiveness of these medications. It is known, for example, that "rescue" by 5-formyl-tetrahydrofolate (a biologically active reduced folate derivative that can compete with antifolate compounds and does not require the activity of the enzyme dihydrofolate reductase for conversion to an active form) is used in patients undergoing chemotherapy with the antifolate Methotrexate. Treatment with 5-formyl-tetrahydrofolate is used to reduce the toxicity of Methotrexate and to protect nonmalignant cells (for example, those in the intestinal tract) from damage by the chemotherapeutic agent.

3. Identifying and targeting the population at risk

a. *The target population*. Given the absence of biological markers to identify women at greatest risk of a neural tube defect pregnancy, a very large population of women must be reached in attempts to reduce the risk of neural tube defects. There are about 70 million women of reproductive age in the United States, of whom about 2,500 annually will have a pregnancy complicated by a neural tube birth defect. As noted above, this number is an underestimate of the number of neural tube defect pregnancies that occur. The safety issues show the importance of the method of implementation chosen to reach the target population. Fortification of the food supply, for example, would expose more than 250 million people to increased folic acid intakes to reach the approximately 4 million women who become pregnant each year. Use of supplements, while potentially capable of targeting some of the population at risk, would not likely reach those of lower socioeconomic status or noncompliers who might also be at increased risk.

b. *Estimation of the "folic acid-preventable" fraction of neural tube defects*. The folic acid-protective effects against risk of neural tube defects found in studies of folic acid at levels lower than 1 mg/day have ranged from none to substantial (Ref. 1). In general, observational studies in areas of moderate prevalence (2-5 neural tube defects/1,000 births) have found protective effects, while a study in two areas of lower prevalence (less than 1 neural tube defect/1,000 births) found no protective effect. While such considerations should not negate an appropriate recommendation for women of child-bearing age, the magnitude of the preventable fraction may influence decisions on how best to implement the PHS recommendation and thus whether and how to provide for a health claim.

4. How does the available information on effective levels of intake effect options for implementation

The neural tube forms and closes during the first month after conception before most women are aware of their pregnancy. For this reason, and since more than half of the pregnancies in the United States are unplanned (Ref. 119), the PHS recommendation stated that it would be prudent for women to consume 0.4 mg of folic acid daily on a regular, continuous basis as long as they are capable of becoming pregnant (Ref.1).

In the supplementary information accompanying its recommendation, the PHS noted that it is possible that lower intakes of folic acid may reduce the risk of neural tube defects, but that further research would be needed to learn the minimum effective level (Ref. 1). This issue is of importance not only because supplement doses lower than 0.4 mg (400 μg) have not been studied adequately, but because of the unknown contribution of dietary intake to the results reported in the available studies. Most of the studies of supplement use have not evaluated folate intake from foods. Thus, the base of dietary folate intake to which folic acid-containing supplement was added is unknown. This complicates assessment of intake-response relationships.

Consideration of the minimum effective level of intake is also relevant because of the need for women to maintain good folate nutriture at least 1 month before conception and through the first 6 weeks of pregnancy. Given this fact and the high rate of unplanned pregnancies in the United States, women potentially must consume an effective amount of folic acid during all or most of their child-bearing years. This represents 30 years or more of chronic exposure for the target population. If the minimum effective

level is added to the conventional food supply, it represents a lifetime of exposure for the entire population.

The best available studies used daily intakes of folic acid of 0.8 mg (800 μg) or 4 mg (4,000 μg). These levels are outside of the range of folate provided by usual U.S. diets. (100 to-500 μg/day). For example, the well-conducted Medical Research Council trial demonstrated that 4 mg of folic acid daily during the periconceptional period, was effective in women at high risk of a recurrence of a neural tube defect-affected pregnancy (Ref. 6). Preliminary data from the recently closed Hungarian trial in women at risk of occurrence of a neural tube defect pregnancy showed that periconceptional use of 800 μg folic acid in a multivitamin/multimineral preparation significantly reduced these defects (Ref. 30). Under current regulations, products with these dosages are drugs.

Based on a synthesis of information from several studies, including those that recorded use of multivitamins containing folic acid at varying doses, the PHS inferred that folic acid at levels of 0.4 mg per day will reduce the risk of neural tube defects (Ref. 1). This level is currently regulated as a food.

Whether other vitamins have an impact on the effect of folic acid when taken at low doses is not known. For example, Smithells et al. (Ref. 8) used 360 μg folic add with other vitamins, and the Hungarian study (Refs. 27 and 30) used a dose of 800 μg folic acid with other vitamins. The study of Milunsky et al. (1989) (Ref. 13)examined folic acid as a component of multi vitamins and Mulinare et al. (1988) (Ref. 12) studied vitamin use but there was no documentation of folic acid use. All preparations associated with reductions in risk of neural tube defects, with the exception of preparations used in the Medical Research Council trial, contained (at least) vitamin A, vitamin D, thiamin, riboflavin, pyridoxine, vitamin C, and niacin in addition to folic acid. The results of Mills et al. (1989) (Ref. 10) showed no effect of folic acid from multivitamins or fortified cereals at a level of 400 μg. Information from a recent case-control study in Boston, Philadelphia, and Toronto suggested that a daily intake of 300 to 400 μg/day of folates from conventional foods offered significant protection from risk of neural tube defects (Ref. 31.). The interrelation between several vitamins and folic acid may be explored by the advisory committee.

The difficulties in identifying a minimal potentially protective intake of folic acid are related in part to observations that poor folic acid status per se is not directly related to neural tube defects (that is, a dietary insufficiency of folic acid has not been consistently associated with increased risk of neural tube defects or predictive of women who would be most likely to benefit from folic acid supplementation). Neural tube birth defects are not among adverse pregnancy outcomes that have been associated with clinical folate deficiency in humans. Inconsistent results have been obtained in clinical studies, carried out to determine if mild to moderate folate deficiency is associated with adverse pregnancy outcomes (Ref. 28).

For example, Yates et al. (1987) (Ref. 16) reported that although erythrocyte folate levels were lower in women who had several infants with neural tube defects, there was no association between erythrocyte folate levels and dietary folate intake. Thus, the risk for recurrence of a neural tube defect pregnancy could not be attributed to lower dietary folate intakes by mothers of affected infants (Ref. 16). Mills et al. (1992) (Ref. 37) recently measured levels of folate, vitamin B_{12} and retinol in maternal serum samples drawn early in 89 pregnancies resulting in neural tube defect offspring and in 178 control pregnancies. Samples were obtained within 8 weeks of neural tube closure. The results of this population-based study in Finland, a low prevalence area for neural tube defects, demonstrated no relationship between maternal serum folate, vitamin B_{12}, and retinol during pregnancy and the risk of neural tube defects.

Nutrition during early pregnancy is critical for normal embryonic development. Human intervention and observational studies have focused on the periconceptional interval as a time when maternal nutritional status is particularly important, and when intervention may be of greatest value. In human embryogenesis, the neural tube forms and closes within the first month of pregnancy, often before a women realizes that she is pregnant.

5. Options for implementation

The supplementary information accompanying the PHS recommendation stated that there are three potential approaches for the delivery of folic acid to the general population in the dosage recommended. These include: (1) Improvement of dietary habits, (2) fortification of the U.S. food supply, and (3) use of dietary supplements. Each option has certain advantages and disadvantages. A careful review of these options is warranted as the agency works toward deciding whether and how to authorize a health claim.

V. Role of the Advisory Committee

Given the significance of neural tube defects and the recommendation of the PHS, FDA convened an advisory committee to help resolve the outstanding concerns on the effects of food claims describing the effects of folic acid intake on neural tube defects. The process that the agency has instituted and the concerns that need to be addressed and resolved are described below.

In addition to convening the advisory committee, the agency will conduct an indepth analysis of consumption patterns for specific foods across all age groups and both genders. The agency will consider various possibilities for fortification of foods, and such analysis will facilitate a determination of the effects of fortification of specific foods on overall intake in selected groups in the population.

The advisory committee heard testimony from experts as well as from other interested parties and provided recommendations to the agency on four broad issues:

(1) What is the target population that needs to be reached regarding the effects of folic acid on neural tube defects?

(2) How does the available information on the effective level of intake affect options for implementation?

(3) What ere the safety concerns for persons in the target population and in the general population?

(4) If a claim is to be authorized, what is the most appropriate method for presenting it to the target population?

An announcement of the meeting of the advisory committee and an opportunity to participate was provided in a **Federal Register** notice (57 FR 52781, November 5, 1992). The agency is reviewing the recommendations provided by the advisory committee.

VI. Impact Statements

A. Economic Impact

In its food labeling proposals of November 27,1991 (56 FR 60366 et seq.), FDA stated that the food labeling - reform initiative, taken as a whole, would have associated costs in excess of the $100 million threshold that defines a major rule. Thus, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA developed one comprehensive regulatory impact analysis (RIA).that presented the costs and benefits of all of the food labeling provisions taken together. That RIA was

published in the **Federal Register** of November 27, 1991 (56 FR 60856). The agency requested comments on the RIA along with the food labeling proposals.

FDA has evaluated more than 300 comments that it received in response to the November 1991 RIA. FDA's discussion of these comments is contained in the agency's final RIA published elsewhere in this issue of the **Federal Register**. In addition, FDA will prepare a final regulatory flexibility analysis (RFA) subsequent to the publication of the food labeling final rules. The final RFA will be placed on file with the Dockets Management Branch (HFA-305). Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, and a notice will be published in the **Federal Register** announcing its availability.

In the final RIA, FDA has concluded, based on its review of available data and comments, that the overall food labeling reform initiative constitutes a major rule as defined by Executive Order 12291. Further, the agency has concluded that although the costs of complying with the new food labeling requirements are substantial, such costs are outweighed by the public health benefits that will be realized through the use of improved nutrition information provided by food labeling.

B. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 101 is amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 continues to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs 201, 301, 402, 403, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 371).

2. Section 101.71 is amended by adding new paragraph (c) to read as follows:

§ 101.71 Health claims: claims not authorized.

* * * * *

(c) Folic acid and neural tube defects.

Dated: December 17, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services

Note: The following table will not appear in the annual Code of Federal Regulations.

BILLING CODE 4160-01-F

Table. Estimates of intakes resulting from fortification of foods with folic acid

Folate/folic acid source	Amount (µg)	Estimate of bioavailability[1] (percent)	Free folic acid equivalent (µg)
Estimate A:			
Usual diet	300	50	150
Add foods fortified to unit limit of 400 µg:			
Plus 1 supplement	400	100	400
Plus 5 servings breads and cereals	2,000	75	1,500
Plus 2 servings fruit juice	800	75	600
Plus 3 servings dairy products	1,200	75	900
Total µg/day	4,700		3,550
Estimate B:			
Usual diet	300	50	150
Add foods fortified to unit limit of 400 µg:			
Plus 2 supplements	800	100	800
Plus 10 servings breads and cereals			
Plus 4 servings fruit juice	1,600	75	1,200
Plus 6 servings dairy products	2,400	75	1,800
Total µg/day	9,100		6,950

[1]Estimates of bioavailability used in FDA's calculation were 50 percent for food folates, 75 percent for folic acid added to foods, and 100 percent for folic acid in supplements.

[FR Doc. 92-31513 Filed 12-28-92; 8:45 am]

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