

[FR Doc. 93-25078 Filed 10-7-93; 2:51 pm]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 93N-0289]

RIN 0905-AD96

Food Labeling; Health Claims for Dietary Supplements

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing not to authorize health claims relating to an association between fiber and cancer, fiber and heart disease, antioxidant vitamins and cancer, *omega-3* fatty acids and coronary heart disease, and zinc and immune function in the elderly on the label or in the labeling of dietary supplements of vitamins, minerals, herbs, or other similar nutritional substances. The agency has tentatively determined that there is not significant scientific agreement among experts that claims on these nutrient-disease relationships are supported by the totality of publicly available scientific evidence. Thus, the agency is proposing to amend its regulations to make it explicit that health claims on these nutrient-disease relationships are not authorized for foods in conventional food form or for dietary supplements. Elsewhere in this issue of the *Federal Register* FDA is proposing to authorize a health claim with respect to the relationship of folic acid and neural tube defects on the labels and in the labeling of dietary supplements and of foods in conventional food form.

DATES: Written comments by December 13, 1993.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12340 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Judith W. Riggins, Office of Policy (HF-23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2831.

SUPPLEMENTARY INFORMATION:

I. Background

A. Passage of 1990 Amendments

On November 8, 1990, the President signed into law the Nutrition Labeling

and Education Act of 1990 (the 1990 amendments) (Pub. L. 101-535), which amended the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorized the Secretary of Health and Human Services (the Secretary), and FDA by delegation, to issue regulations authorizing health claims on the label or labeling of foods. Under these new health claim provisions, a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under sections 403(r)(3) and (r)(5)(D) of the act (21 U.S.C. 343(r)(3) and (r)(5)(D)).

The 1990 amendments also required (section 3(b)(1)(A)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x)) that the Secretary issue proposed regulations to implement section 403(r) of the act. These provisions also required the Secretary to determine through rulemaking, among other things, whether claims regarding 10 nutrient-disease relationships met the requirements of the act. FDA was asked to evaluate the scientific evidence for the relationships: (1) Dietary fiber and cancer; (2) dietary fiber and cardiovascular disease (CVD); (3) folic acid and neural tube defects; (4) antioxidant vitamins and cancer; (5) zinc and immune function in the elderly; (6) *omega-3* fatty acids and coronary heart disease (CHD); (7) calcium and osteoporosis; (8) dietary lipids and CVD; (9) dietary lipids and cancer; and (10) sodium and hypertension.

B. The 1991 Health Claims Proposals

In the *Federal Register* of November 27, 1991 (56 FR 60537), FDA proposed general requirements regarding the use of health claims on the labels of both conventional foods and dietary supplements and regarding the content of petitions requesting the use of health claims related to specific substances in food. FDA also published proposals on health claims on the 10 nutrient/disease topics listed above.

Based on its review of the available scientific information, FDA tentatively found that four relationships were supported, and it proposed to allow health claims on food labels for calcium and osteoporosis, sodium and hypertension, fat and cardiovascular disease, and fat and cancer. FDA conditionally concluded that two other claims—fiber and heart disease and fiber and cancer—required additional information. Additionally, because sufficient scientific information was lacking, FDA proposed not to permit

claims for four nutrient disease relationships: folic acid and neural tube defects; antioxidant vitamins and cancer; zinc and immune function in the elderly; and *omega-3* fatty acids and heart disease.

C. The Dietary Supplement Act of 1992

In October 1992, the Dietary Supplement Act (the DS Act) (Pub. L. 102-571) was enacted. This statute imposed a moratorium on FDA's implementation of the 1990 amendments with respect to dietary supplements until December 15, 1993. The DS Act required FDA to issue proposed rules to implement the 1990 amendments with respect to such dietary supplements by June 15, 1993, and to publish the final rules based on these proposals by December 31, 1993. An exception to this moratorium was a provision that permitted FDA to authorize health claims for dietary supplements with respect to those nutrient-disease relationships for which the agency authorized claims on foods in conventional food form. The DS Act also amended the 1990 amendments to state that if the agency did not meet the established timeframe for issuance of final rules with respect to health claims on dietary supplements, the proposed regulations would be considered final regulations.

D. The 1993 Final Rules for Health Claims for Foods in Conventional Food Form

On January 8, 1993, FDA published final rules on the general requirements for health claims on the labels and in the labeling of foods in conventional food form (58 FR 2478) and final rules authorizing health claims on seven nutrient/disease relationships (calcium and osteoporosis; fat and cancer; saturated fat and cholesterol and CHD; fiber-containing grain products, fruits, and vegetables and cancer; fruits, vegetables and grain products that contain fiber and risk of CHD; sodium and hypertension; and fruits and vegetables and cancer).

It should be noted that of the seven health claims that FDA authorized, three were for fresh fruits and vegetables and grains, and thus these claims are not authorized on dietary supplements. FDA will be considering the nutrient-disease relationships that led the agency to authorize these claims, fiber and cancer, fiber and CHD, and antioxidant vitamins and cancer, as well as two others, *omega-3* fatty acids and CHD and zinc and immune function in the elderly, for dietary supplements in this document. FDA will consider the evidence on folic acid and neural tube

defects in a document published elsewhere in this issue of the Federal Register.

E. The 1993 Proposed Rules for Health Claims on Dietary Supplements

In response to the 1990 amendments and the DS Act, FDA proposed in the Federal Register of June 18, 1993 (58 FR 33700), to revise its food labeling regulations to make dietary supplements of vitamins, minerals, herbs, and other similar nutritional substances subject to a standard and procedure for the use of health claims that characterize the relationship of a substance to a disease or health-related condition on the label or in labeling that are the same as those that Congress established for foods in conventional food form.

The agency did not address the specific nutrient-disease relationships for nutrients in dietary supplements that it is required to consider under sections 3(b)(1)(A)(vi) and (b)(1)(A)(v) of the 1990 amendments and under the DS Act. It stated that it would address these relationships in the near future. It is doing so in this document and the companion document on folic acid and neural tube defects that is published elsewhere in this issue of the Federal Register.

F. Provisions of the Proposed Rule—Regulation Amended

Section 101.71(a) (21 CFR 101.71(a)) of the January 6, 1993, final rule specified that the agency had not authorized health claims on the label or in the labeling of foods in conventional food form for six nutrient-disease relationships: Fiber and cancer; fiber and heart disease; antioxidant vitamins and cancer; omega-3 fatty acids and CHD; folic acid and neural tube defects; and zinc and immune function in the elderly.

In this document, FDA is proposing to amend § 101.71(a) to state that health claims regarding five of these nutrient-disease relationships are not authorized for foods in conventional food form or for dietary supplements of vitamins, minerals, herbs, or other similar substances. Elsewhere in this issue of the Federal Register FDA is proposing to remove the sixth, folic acid and neural tube defects, from the list.

II. Dietary Fiber and Cancer

A. The 1991 Proposed Findings

In the Federal Register of November 27, 1991 (56 FR 60566), FDA published a proposal on the use of a health claim regarding the relationship of dietary fiber and cancer. After reviewing the available scientific evidence, it

tentatively found that there was not a sufficient basis to authorize the use of health claims regarding the relationship of dietary fiber and a reduction in the risk of cancer on the labels or in the labeling of foods, including dietary supplements. The agency tentatively found that while data supported an association between consumption of fiber-rich plant foods and a reduced risk of cancer, they did not establish a basis on which to find that this effect was attributable to the fiber itself.

FDA limited its review of the scientific evidence relating ingestion of dietary fiber and cancer to the topic of dietary fiber and the risk of colorectal cancer. FDA deemed this limitation appropriate because the great majority of epidemiologic and intervention studies have focused on colon cancer, as have virtually all animal studies on this topic. The strongest support and largest volume of evidence for a possible protective effect of fiber-rich diets is for colon and rectal cancers (colorectal cancer), the second leading causes of cancer deaths in the United States. FDA found that relationships between dietary fiber and the risk of cancer at other sites (for example, breast, stomach, endometrium, and ovaries) had been less extensively examined but were the focus of considerable research effort (56 FR 60566 at 60576).

In deciding whether to authorize a claim relating dietary fiber to cancer, FDA considered all available evidence on this topic, including extensive review of consensus documents like "The Surgeon General's Report on Nutrition and Health," the National Academy of Sciences' "Diet and Health, Implications for Reducing Chronic Disease Risk," and other relevant reports and other reviews by recognized scientific bodies (56 FR 60566 at 60569 and 60570) and reports in the scientific literature.

FDA cited several key factors (56 FR 60566 at 60576 and 60577) that formed a basis for its tentative conclusion that the use of a health claim relating the intake of fiber to a reduced risk of cancer was not sufficiently supported by scientific evidence. These factors included: (1) The fact that the prospective epidemiologic studies that exist are few in number and have had mixed results; (2) insufficient data exist to demonstrate that it is the total dietary fiber, or a specific fiber component, that is related to any reduction of cancer risk; (3) the need for better defined measures of dietary fiber and for standardized descriptions of the source, type, and amount of dietary fiber; and (4) a lack of composition data on the fiber content of foods that precluded

estimates of dietary intakes of total dietary fiber or fiber components in most human studies (56 FR 60566 at 60577 and 60578).

B. The January 1993 Final Rule

In the Federal Register of January 6, 1993 (58 FR 2537), FDA published a final rule that announced its decision to authorize a health claim regarding the relationship of diets low in fat and high in fiber-containing grain products, fruits, and vegetables to a reduced risk of cancer. The agency reviewed numerous authoritative documents, as well as more recent research on dietary fiber and cancer risk (58 FR 2537 at 2542 and 3543). In addition, the agency reviewed the comments that it had received on the November 1991 proposal (58 FR 2537 at 2540 and 2541). The agency concluded that the publicly available scientific evidence supports an association between diets low in fat and high in fiber-containing grain products, fruits, and vegetables and reduced risk of cancer (58 FR 2537 at 2544). FDA explained the basis for this conclusion, listed the elements that had to be addressed in any health claim, listed the circumstances in which a food would be eligible to bear a claim, provided for additional optional information that could be included as part of the claim, and set out two model health claims that could be used on labeling (58 FR 2537 at 2544 to 2545).

The agency went on to state, however, that based on the totality of the publicly available scientific evidence, including recently available evidence, there was not significant scientific agreement among qualified experts that a claim relating dietary fiber, per se, to a reduced risk of cancer was scientifically valid. FDA reviewed the new scientific evidence, including studies that focused on prior cholecystectomy as a risk factor for right-sided colon cancer (58 FR 2537 at 2542); colonic adenoma incidence based on sigmoidoscopy biopsy reports (58 FR 2537 at 2543); dietary factors in a case-control study of colonic polyp patients (58 FR 2537 at 2543); rectal cell proliferation, fecal bile acid concentration, and fecal pH (58 FR 2537 at 2543); fecal short-chain fatty acid composition in controls and patients with resected adenomatous polyps and resected colonic cancer (58 FR 2537 at 2543); and the effect of fat and cellulose fiber on the growth and biochemical characteristics of two human colon cancer cell lines implanted subcutaneously in mice (58 FR 2537 at 2543). These new studies provided data on the possible link between consumption of dietary fiber and reduced risk of colon cancer. However,

with the exception of one study that had limited applicability (see 58 FR 2537 at 2543), none of the studies provided evidence of an independent contribution of fiber itself (distinct from its presence in food) to risk reduction. Rather, the studies showed a relationship between diets rich in fiber-containing foods and a reduced risk of cancer (58 FR 2537 at 2543). In addition, preliminary results of a study on the effects of amount and type of dietary fiber on colonic bacterial enzymes and bile acids in humans supported FDA's observation that insoluble fiber has not been shown to be protective (58 FR 2537 at 2543).

In addition to these factors, the agency's decision was based on the absence of a well-defined measure of dietary fiber and of standardized descriptions of source, type, and amount of dietary fiber. The agency identified factors, including the inability of commonly used methodologies to detect variable characteristics of fiber (e.g., particle size and chemical composition), the inability to identify the characteristics among fibers that are predictive of physiological effects, and the general lack of clear evidence on the mechanisms of action of fibers, that made it difficult to establish the role of fiber in the health effects of diets that are low in fat and high in fiber-rich foods (58 FR 2537 at 2544).

The full discussion from the proposed and final rules, including the studies cited in those documents is referenced herein.

C. Summary of Comments

In issuing the final rules in January of 1993, the agency recognized that an undertaking of the magnitude of the agency's rulemaking under the 1990 amendments was bound to include certain unintended technical problems. Therefore, the agency invited comments on technical matters and addressed them in technical amendment final rules in the Federal Register of June 18, 1993 (58 FR 33700).

Two comments requested clarification of the term "without fortification" as used in the final rules. One of these comments also requested clarification that the use of fiber-containing ingredients in bakery products that already contain fiber does not constitute fortification. Another comment stated that in the agency's discussion of dietary fiber in its final rule on mandatory nutrition labeling, it equated "fortification" with "supplementation," a definition that connotes an addition to a fiber source so that the resulting level of fiber in that source exceeds the

indigenous level (58 FR 2079 at 2096, January 6, 1993). Therefore, the comment asked FDA to clarify that the combination of multiple grains in a food, each of which contains an indigenous level of fiber, is not fortification as the agency used the term in its final rule.

The questions raised in these comments specifically request clarification of the agency's criteria regarding the definition of "fortification." These comments are not relevant to the issue of whether the agency may authorize a health claim on the relationship of dietary fiber to cancer. Therefore, the agency will address these comments in a separate Federal Register document.

The agency did not receive any comments that provided any information that would support a health claim on the labels or in the labeling of dietary supplements regarding the relationship of dietary fiber and reduced risk of cancer in response to the January 6, 1993, final rule. Thus, the agency is not aware of any basis to find that a different conclusion than it reached in January 1993 is appropriate on whether to authorize a claim on fiber, specifically the fiber in dietary supplements, and the risk of cancer.

D. The Proposal

Based on the totality of the publicly available scientific evidence, FDA has tentatively concluded that there is not significant scientific agreement among qualified experts that a health claim on the labels or in the labeling of dietary supplements regarding the relationship of dietary fiber and reduced risk of cancer is scientifically valid. Numerous human and animal studies have examined the possible role of dietary fiber intake in reducing the risk of developing cancer. Most correlational and many (but not all) case-control studies show that diets high in fiber-containing foods (whole grains, fruits, and vegetables) are associated with reduced risk of colorectal cancer. These diets differ, however, in levels of many nutrients and types of dietary fiber, making it difficult to ascribe the observed nutrient and disease relationship to a single nutrient. Overall, the available data are not sufficiently conclusive or specific for fiber to justify authorization of a health claim relating the intake of dietary fiber to a reduced risk of cancer on the labels or in the labeling of dietary supplements.

Because a supplement would contain only fiber, and there is no evidence that any specific fiber itself caused the effects that were seen in studies

involving fiber-rich fruits, vegetables, and grain products, FDA tentatively finds that an appropriate basis for proposing to authorize a claim on dietary fiber and cancer on dietary supplements does not exist (56 FR 60566 and 58 FR 2537).

III. Dietary Fiber and Cardiovascular Disease

A. The 1991 Proposed Findings

In the Federal Register of November 27, 1991 (56 FR 60582), FDA published a proposal on the use of a health claim regarding the relationship of dietary fiber and cardiovascular disease. After reviewing the available evidence, it tentatively concluded that there was no basis to authorize such health claims on the labels or in labeling of foods, including dietary supplements. The agency tentatively found that while an association appeared to exist between the consumption of fiber-rich foods and a reduced risk of cardiovascular disease, the data did not provide a basis on which it could not attribute this effect to the fiber itself (56 FR 60582).

FDA limited its review of the scientific evidence related to ingestion of dietary fiber and cardiovascular disease to the topic of soluble dietary fiber and risk of developing CHD. Previous Federal government and other reviews by recognized scientific bodies and the majority of research efforts had focused on this topic. Therefore, FDA tentatively concluded that this limitation was appropriate (56 FR 60582 at 60592).

In deciding whether to authorize a claim relating dietary fiber to cardiovascular disease, FDA considered all available information on this topic, including the incidence of cardiovascular disease in the United States, current chemical information on dietary fiber and analytical methodology used to determine the biological and health consequences of dietary fiber intake, and all available information on the risk factors that contribute to CHD (56 FR 60582 at 60583). FDA also considered recent Federal government comprehensive reports, reviews, and dietary guidelines on this topic (56 FR 60582 at 60584). The agency's tentative conclusion that the totality of the evidence did not provide a sufficient basis to authorize a health claim on dietary soluble fiber and reduction in risk of developing CHD was based on its tentative finding that while many human studies showed a relationship between diets high in plant foods (e.g., fruits, vegetables, and grains) and a reduced risk of developing CHD, these diets differed in the levels of many

nutrients and in types of dietary soluble fiber, making it difficult to ascribe the observed effects to a single nutrient (56 FR 60582 at 60592).

FDA reviewed over 30 human studies published in the United States over the last several years. Under the study conditions, many investigators observed a decline in blood cholesterol levels with increasing intakes of soluble fiber. Most studies, however, were of very short duration and, therefore, could not establish long-term benefits from high soluble fiber diets. Questions of long-term effects were raised by the observation of an initial decline in blood cholesterol levels followed by a return upwards towards baseline in some of the longer studies, even when the investigators reported excellent compliance for consumption of test substances (56 FR 60582 at 60591).

Based on the studies it reviewed, FDA tentatively concluded that serum cholesterol responses were affected by a number of factors, including initial serum cholesterol level, base diet, self-initiated changes to base diet (particularly changes in intake of saturated fat and polyunsaturated fat) during the test period, body weight, exercise, medications, general health, and other lifestyle variables. These confounding factors, which were generally not well controlled within the individual studies and which made cross-study comparisons difficult, made it impossible to draw conclusions about the relationship of fiber intake to serum cholesterol levels (56 FR 60582 at 60593).

FDA cited certain additional factors that contributed to its tentative conclusion that the available data did not demonstrate that soluble dietary fiber, or a specific measurable and quantifiable subcomponent of dietary fiber, is related to lower blood cholesterol levels (56 FR 60582 at 60592). These factors included: (1) The need for better defined measures of dietary fiber and for standardized descriptions for source, type, and amount of dietary fiber; and (2) a lack of composition data on the fiber content of foods that precluded estimates of dietary intakes of total dietary fiber or fiber components in most human studies (56 FR 60582 at 60593 through 60595).

B. The January 1993 Final Rule

In the *Federal Register* of January 6, 1993 (58 FR at 2552), FDA published a final rule announcing its decision to authorize a health claim regarding the relationship of diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that

contain dietary fiber (particularly soluble fiber) and a reduced risk of CHD. The agency reviewed numerous authoritative documents, as well as recent research on dietary fiber and CHD risk (58 FR 2552 at 2552 through 2562). In addition, the agency reviewed the comments that it received (58 FR 2552 at 2562 through 2572).

FDA concluded that the publicly available scientific evidence supports an association between diets low in saturated fat and cholesterol and high in fruit, vegetables, and whole grains that contain soluble fiber to a reduced risk of CHD (58 FR 2552 at 2572). The agency explained the basis for its conclusion and set out the elements that had to be addressed in any health claim (58 FR 2552 at 2572 through 2574).

In the same document (58 FR 2552), FDA announced its decision to not authorize the use of health claims regarding the relationship of dietary fiber and a reduced risk of CHD on the label and labeling of foods. FDA found that the available scientific evidence was not sufficiently conclusive or specific for soluble fiber to justify use of a health claim for this relationship (58 FR 2552 at 2572).

FDA reviewed new scientific evidence including studies on mildly to moderately hypercholesterolemic individuals and normocholesterolemic individuals using multiple sources of soluble fiber, including oat bran and other cereal brans, legumes, pectin, psyllium, and guar gum (58 FR 2552 at 2553 through 2558). The agency noted that the studies had significant design flaws, including very small sample sizes; inadequate control of confounding factors, such as concomitant weight losses and changes in other dietary components, that may have affected some studies; and the absence of adequate data to ensure that dietary changes other than differences in soluble fiber intakes had not occurred. The agency determined that, given inconsistencies in results among similar studies using apparently similar fibers, the physiological effects of particular fibers were not consistently predictable by an analytical definition of dietary fiber but rather varied, in some unknown way, among different sources or combinations of sources of dietary fiber. Therefore, the agency concluded that generalizing results from one type of fiber source to another in determining whether the relationship between soluble fiber and heart disease is supported by the evidence requires caution (58 FR 2552 at 2559).

The agency also reviewed new animal studies on the relationship between specific soluble fibers and plasma

cholesterol and the relationship between *beta*-glucan and plasma cholesterol (58 FR 2552 at 2559 through 2562). The agency determined that these studies provided evidence to support the likely effectiveness of soluble fibers relative to the cholesterol-lowering characteristics of diets high in some cereals. However, the animal studies, like the human studies, failed to provide adequate specifications to characterize the test fiber sources and did not provide characteristics or commercial sources of the soluble fibers used as test substances (58 FR 2552 at 2562).

Therefore, the agency concluded that, overall, the available data were not sufficient to demonstrate that it is total soluble dietary fiber, or a specific measurable and quantifiable subcomponent of that fiber, that is related to lower blood cholesterol levels (58 FR 2552 at 2562). The full discussion from the proposed and final rules, including the studies cited in those documents, is referenced herein.

C. Summary of Comments

In issuing the final rules in January of 1993, the agency recognized that an undertaking of the magnitude of the agency's rulemaking under the 1990 amendments was bound to include certain unintended technical problems. Therefore, the agency invited comments on technical matters and addressed them in technical amendment final rules in the *Federal Register* of June 18, 1993 (58 FR 33700).

The only comments that FDA received about fiber were those that it described in its discussion of fiber and cancer. The agency did not receive any comments that provided information that would support a health claim on the labels or in the labeling of dietary supplements regarding the relationship of dietary fiber and reduced risk of cardiovascular disease, including CHD, in response to the January 6, 1993, final rule. Thus, the agency is not aware of any basis to find that a different conclusion than it reached in January 1993 is appropriate on whether to authorize a claim on dietary supplements on this nutrient-disease relationship.

D. The Proposal

Based on the totality of publicly available scientific evidence, FDA has tentatively concluded that there is not significant scientific agreement among qualified experts that a health claim regarding the relationship of dietary fiber and reduced risk of cardiovascular disease on the labels or in the labeling of dietary supplements is valid

A major limitation in designing and evaluating research studies has been the need for better defined measures of dietary soluble fiber and standardized descriptions of source, type, and amount of dietary soluble fiber. Commonly used analytical methodologies do not detect many of the characteristics that may vary among fibers and that may be related to biological function. Other components associated with soluble fibers in foods may also have some ability to affect blood cholesterol levels. The inability to detect many of the differences among fibers, fiber components, and other substances in foods that contain soluble fiber, and the general lack of conclusions regarding the mechanisms of action of soluble fibers, raise questions about the ability of commonly used analytical methods to adequately predict biological actions of specific fibers. The currently available scientific evidence is not sufficiently conclusive or specific for soluble fiber to justify use of a health claim relating the intake of dietary fiber to a reduced risk of cardiovascular disease, including CHD.

Because a dietary supplement would contain only fiber, and there is no evidence that the fiber itself caused the effects that have been seen in studies of diets low in saturated fat and cholesterol and high in fruits, vegetables, and whole grains, FDA tentatively finds that an appropriate basis for proposing to authorize a claim on dietary fiber and cardiovascular disease on dietary supplements does not exist (56 FR 60582 and 58 FR 2552).

IV. Antioxidant Vitamins and Cancer

A. The 1991 Proposed Findings

In the Federal Register of November 27, 1991 (56 FR 60624), FDA published a proposal on the use of a health claim regarding the relationship of antioxidant vitamins and cancer. In deciding whether to authorize a claim, FDA examined all available information on this topic (56 FR 60624 at 60625 and 60626), including the mechanisms of carcinogenesis and its relationship to antioxidants, the interactions among antioxidants, and the associations between *beta*-carotene and risk of cancer (56 FR 60624 at 60627). The agency also considered the regulatory history of antioxidant vitamins and all comments that it had received in response to a request for scientific data and information (56 FR 60624 at 60628 and 60629).

The agency tentatively found that there was no basis to authorize such claims regarding the relationship of antioxidant vitamins and cancer on the

labels and in the labeling of foods. The agency found that strong epidemiologic evidence existed that showed that consumption of fruits and vegetables, which tended to contain higher amounts of vitamin C, were associated with reduced risk of cancers in some sites, notably the stomach and gastrointestinal tract. However, the agency also tentatively found that it was not possible to determine from the available data whether the reduced risks of cancer at specific sites were caused by the vitamin C content of the foods, by other components that were present in those foods, or by general dietary patterns that included those foods (56 FR 60624 at 60636). The agency further recognized that consumption of food sources of vitamin E was frequently, but not consistently, associated with lowered risk of cancer at a number of sites. However, the agency tentatively concluded that the data did not demonstrate that vitamin E itself was responsible for this association, and that the data did not permit identification of the other factors that might produce or prevent the effect. In addition, the agency tentatively found that the data were insufficient to determine the amount of vitamin E needed to produce the effect (56 FR 60624 at 60638).

B. The January 1993 Final Rule

In the Federal Register of January 6, 1993 (58 FR 2622), FDA published a final rule that announced its decision to authorize a health claim regarding the relationship of diets low in fat and high in fruits and vegetables (foods that are low in fat and may contain dietary fiber, vitamin A, and vitamin C) to a reduced risk of cancer. The agency reviewed numerous authoritative documents as well as new studies on the association of intake of *beta*-carotene, vitamin C, and vitamin E and the risk of cancer (58 FR 2622 at 2623 through 2627 and 2636 through 2639). The agency also reviewed the comments on this relationship that it had received (58 FR 2622 at 2627 through 2633). The agency concluded that the publicly available scientific evidence supported an association between diets high in fruits and vegetables that are good sources of two of the antioxidant vitamins (vitamin A as *beta*-carotene and vitamin C) and a reduced risk of cancer (58 FR 2622 at 2633). FDA described the information concerning *beta*-carotene, vitamin C, and fruits and vegetables that served as a basis for its decision (58 FR 2622 at 2633 and 2634) and explained the basis for the requirements that it was establishing for the health claim (58 FR 2622 at 2635 and 2636).

FDA went on to announce (58 FR 2622) its decision not to authorize the use of a health claim regarding the relationship of antioxidant vitamins and cancer on the label or labeling of foods. Based on the totality of the publicly available scientific evidence, including the recently available evidence, the agency concluded that there was not significant scientific agreement among qualified experts as to whether the observed protective effects of fruit and vegetable consumption on cancer risk were the result of a single or combined effect of the antioxidant vitamins and other nutrients with antioxidant functions (i.e., selenium), of unmeasured components of such foods such as nonnutritive components, or of displacement of other known risk components (such as fats and calories) within the total diet (58 FR 2622 at 2634). Therefore, the agency concluded that a claim relating antioxidant vitamins to reduced risk of cancer was not supported by available scientific evidence.

1. Vitamin E

FDA concluded that the available scientific data did not support that there is a relationship between vitamin E and a reduced risk of cancer. Most of the studies on the possible protective effect to vitamin E related plasma or serum levels of vitamin E (rather than food consumption) to cancer risk. FDA recognized that some evidence showed an association of low plasma serum levels of vitamin E and an increased cancer risk. The agency found, however, that the available evidence was not adequate to determine whether this association was the result of an effect specific to vitamin E or the result of other unmeasured factors that are associated with those dietary patterns that would produce such plasma serum levels (58 FR 2622 at 2633). FDA recognized that the animal data and biochemical data provided a basis on which to hypothesize a protective effect of vitamin E (*alpha*-tocopherol) in humans but found that the data from epidemiological studies, although providing some suggestion of an effect, were not sufficient to conclude that such effects were of importance in humans. Therefore, the agency concluded that, although vitamin E has been shown to have an antioxidant effect in humans, the data were not sufficient to associate such effects with protection against cancer (58 FR 2622 at 2633).

2. Beta-carotene

Based on the totality of the scientific evidence and comments that it received

relative to the available evidence, FDA concluded that the data did not support the relationship of *beta*-carotene (provitamin A) to a reduced cancer risk. Although the available scientific human data showed an association of consumption of fruits and vegetables and calculated *beta*-carotene intakes from these foods with reduced risk for some types of cancer, the agency concluded that the available scientific evidence was not sufficient to conclude that the *beta*-carotene, as opposed to some other component of these foods, was responsible for the protective effect (58 FR 2622 at 2633).

Consistent with earlier studies reviewed in the proposed rule (56 FR 60624 at 60634), the more recent studies supported findings that there was an inverse relationship between consumption of fruits and vegetables and the risk of cancer. This relationship was strongest for lung cancer. Intakes of the green and yellow vegetables had also been shown to be inversely associated with cervical cancer, but the evidence was not as consistent as with lung cancer. These studies were based on calculated intakes of nutrients from these foods. However, the agency said that it was not possible to determine from these studies what substance or substances in these foods were responsible for the results. FDA found that *beta*-carotene may have been responsible for the effect, but that its presence in these foods may simply have served as a marker for some other unmeasured substances that were responsible for the protective effect of fruits and vegetables (58 FR 2622 at 2626).

3. Vitamin C

The data reviewed by FDA in the final rule were compatible with the tentative conclusion in the proposed rule that consumption of fruits and vegetables rich in vitamin C might protect against some types of cancer (58 FR 2622 at 2626). These data also provided additional indications of a mechanism to explain the relationship between vitamin C and reduced risk of stomach cancer. The relatively small number of studies reported after the publication of the proposed rule were in agreement with earlier findings that consumption of fruits and vegetables was protective against cancer at several sites, particularly stomach cancer. The new studies, taken together with previous studies, indicated that consumption of fruits and vegetables is most consistently protective against cancers of the stomach, lung and cervix, and less consistently protective at other sites. These data, however, were not

sufficient to identify vitamin C, as opposed to other substances in these foods, as being responsible for the observed protective effect (58 FR 2622 at 2626).

FDA also recognized that the mechanistic and animal studies suggested that vitamin C may reduce the risk of cancer through the mechanism of inhibition of nitrosamine synthesis. The stomach is the likely site of highest *N*-nitroso compound exposure and is the site for which the data were the most complete. These data provided a mechanistic basis for understanding a possible protective effect of vitamin C for stomach cancer risk. However, FDA concluded that nitrosation had not been accepted by the general scientific community as a validated risk factor for stomach cancer. One of the unsolved questions was whether studies of this mechanism for the Chinese and other populations, which differ from the U.S. population in genetic, dietary, and environmental risk factors, adequately explain the etiology of stomach cancer in the United States (58 FR 2622 at 2627).

The studies showing the relationship of *N*-nitroso compounds (a class of compounds with known carcinogenicity) to stomach cancer provided evidence for a mechanism by which a specific vitamin C effect might occur for this and other cancers (e.g., esophageal and uterine cervical). When considered together, the different types of data were suggestive, but not conclusive, that vitamin C may be responsible for at least part of the reduction in risk of stomach cancer associated with consumption of diets high in fruits and vegetables in U.S. populations. Given differences in rates and likely etiologies of stomach cancer among different cultures and geographic areas, FDA concluded that there was not significant scientific agreement either that this mechanism is an etiologic factor in stomach cancer risk in the United States, or that qualitative changes in production and excretion of nitroso-compounds are a risk factor for stomach cancer (58 FR 2622 at 2634).

In order to allow the issue of intermediate or surrogate markers (such as the formation of nitroso-compounds) for cancer risk to be more fully evaluated, FDA stated that it would convene an advisory committee in the near future to make recommendations that could be applied to evaluations of data for determining the scientific basis for health claims relating antioxidant vitamin intakes to cancer risk (58 FR 2622 at 2634).

FDA summarized its considerations of all comments received (58 FR 2622 at

2630 through 2632) and recent scientific evidence (58 FR 2622 at 2633 and 2634) in its examination of the issues. The full discussion from the proposed and final rules, including the studies cited in those documents, is referenced herein.

C. Summary of Comments

In response to the January 6, 1993, final rule, FDA received comments that raised the following concerns: Two comments requested that the agency raise the threshold (percentage of Recommended Dietary Allowance (RDA)) at which a product could bear a health claim. One of these comments also requested that FDA broaden the scope of products that could bear a claim regarding relationship of antioxidant vitamins and a reduced risk of cancer.

A third comment stated that although advisory committees can be helpful in reaching scientific conclusions, the result can be predetermined depending on the persons selected. It urged the agency to make every attempt to ensure that the membership of the committee on antioxidants is balanced to encompass the spectrum of nutritional thought. Another comment stated that the agency should allow consumers to receive accurate and balanced information where there is a reasonably good chance of benefit and virtually no safety risk. Another comment objected to the agency's position in the final rule that it would not be permissible for a health claim to imply that levels clearly beyond the range attainable in the context of the total daily diet would be effective in reducing the risk of a disease or health-related condition, stating that this was an implied premise that products such as vitamins and minerals are not really foods. Another comment requested that the agency provide examples to clarify the meaning of the section of the final rule that requires that qualifying nutrients be based on natural levels in foods.

None of these comments are relevant to the issue of whether there is an appropriate scientific basis for the agency to authorize a health claim on the relationship of dietary fiber to cardiovascular disease, nor did any of them provide any additional information upon which the agency could rely to authorize a health claim for this relationship. Thus, the agency did not receive any information in these comments that would support a different conclusion on a health claim regarding the relationship of antioxidant vitamins and cancer than the one that it reached regarding a health claim on this nutrient-disease relationship for foods

in conventional food form in the January 6, 1993, final rule.

As for the matters that were raised in the comments, the latter comments relate to the standard and procedure for health claims on dietary supplements. These issues will be dealt with by FDA as part of the rulemaking instituted in June by FDA (58 FR 33700). As for the makeup of FDA advisory committees, the agency is required by the Federal Advisory Committee Act to ensure that its advisory committees are balanced, and it always endeavors to ensure that balance in fact exists. The basis on which the agency chose the level necessary to qualify for the health claim was fully explained in the final rule (see 58 FR 2622 at 2636). The comments provided no information that would cause the agency to conclude that the basis that is set out for the amount of vitamin A or vitamin C that must be present in the food for it to qualify for a health claim was not appropriate. Finally, as explained in this document, FDA has not been provided with evidence that would justify broadening the scope of products that could bear the claim.

D. The Proposal

FDA has tentatively concluded, based on the totality of publicly available scientific evidence, that there is not a sufficient basis to authorize a health claim regarding the relationship of antioxidant vitamins and cancer on the labels or in the labeling of dietary supplements. While populations with diets rich in fruits and vegetables experience many health advantages, including lower rates of some types of cancers, it is not possible to specifically determine that the two antioxidant vitamins (*beta*-carotene and vitamin C) that are contained in fruits and vegetables are responsible for this effect or to rule out the possibility of significant protective effects from nonmeasured components in these foods. Since many food substances (both nutritive and nonnutritive) coexist in fruits and vegetables, an observed correlation between a measured nutrient and a disease risk may be a surrogate for a "true" correlation between a coexistent, but a nonmeasured or an unknown, food substance. Currently, there is not significant scientific agreement as to whether the observed protective effects of fruits and vegetables are the result of a single or combined effect of the antioxidant vitamins and other nutrients with antioxidant functions (e.g., selenium), to other nutritive compounds in such foods, to unmeasured components of such diets, or to displacement of other

known risk components within the total diet.

Because a dietary supplement would contain only the antioxidant vitamins, and there is not significant scientific agreement that the antioxidant vitamins alone caused the effects that were observed in the relevant studies, FDA tentatively finds that an appropriate basis for proposing to authorize a claim on antioxidant vitamins and cancer on dietary supplements does not exist (56 FR 60624 and 58 FR 2622).

V. Zinc and Immune Function in the Elderly

A. The 1991 Proposed Findings

In the Federal Register of November 27, 1991 (56 FR 60652), FDA published a proposal on the use of the health claim regarding the relationship of zinc and immune function in the elderly. Based on its review of the available scientific evidence, the agency tentatively concluded that there was not a sufficient basis to authorize the use of a health claim regarding the relationship of zinc and immune function in the elderly on the label or in the labeling of foods. The agency stated that a specific protective role of zinc supplementation of the elderly population had not been demonstrated.

In deciding whether to authorize a claim regarding this nutrient-disease relationship, FDA reviewed all available scientific evidence on this topic, including public health aspects of zinc and immune function in the elderly, mechanisms and measures of immunity, and immune function in aging (56 FR 60652 at 60653). FDA also conducted an extensive review of consensus documents and of reports in the scientific literature (56 FR 60652 at 60653 and 60654 through 60663). In addition, FDA reviewed comments that it received on this nutrient-disease relationship (56 FR 60652 at 60654).

FDA tentatively found that the scientific evidence showed that proper dietary zinc levels are essential for adequate function of the immune system, and that dietary zinc intake, serum zinc, and cell-mediated immunity all decline with advancing age. However, the agency tentatively concluded that the available data did not provide a basis on which to find that increased zinc intake can reverse the age-related decline in immunocompetence in the general healthy elderly population in the United States. In fact, the agency noted that some evidence suggested that it may suppress immune function (56 FR 60652 at 60661).

The data evaluated by FDA included seven human studies in which elderly subjects were supplemented with zinc to determine its influence on immune system function. The results of four of the earliest published studies suggested a zinc-associated enhancement of several measures of immune function. However, FDA noted that the reliability of three of these studies was limited by the fact that they included very few individuals, and by the fact that the tested subjects were not representative of the general elderly population. Moreover, FDA noted that the results of these initial reports have not been substantiated by more recent, larger studies of more rigorous experimental design (56 FR 60652 at 60661).

B. The January 1993 Final Rule

In the Federal Register of January 6, 1993 (58 FR 2661), FDA published a final rule that announced its decision not to authorize the use of a health claim regarding the relationship of ingestion of zinc and immune function in the elderly on the labels or in the labeling of foods in conventional food form. The agency concluded that, based on the totality of the publicly available scientific evidence, there was not significant scientific agreement that increased intake of zinc enhanced immune function in the elderly.

The agency stated that zinc is considered to be relatively nontoxic, particularly if taken orally, but that adverse effects, which include impaired immune function, are known to occur with zinc intake in excess of the RDA. The agency's examination of the scientific evidence found that although it is well accepted that adequate dietary zinc is essential for normal immune function, a specific protective role of zinc supplementation of the elderly population has not been demonstrated.

Thus, FDA concluded that the publicly available data on the role of zinc in immune system function do not provide a sufficient scientific basis on which to conclude that immune function in the elderly U.S. population can be improved by zinc supplementation. On this basis, FDA decided not to authorize the use of a health claim on this nutrient-disease relationship on the label or in labeling of foods in conventional food form.

The agency summarized its consideration of the comments received (58 FR 2661 at 2662) and publicly available scientific evidence (58 FR 2662 at 2663 and 2664) in reaching its conclusion. The full discussion from the proposed and final rules, including the studies cited in those documents, is referenced herein.

C. Summary of Comments

The agency did not receive any comments regarding the relationship of ingestion of zinc and immune function in the elderly in response to the January 6, 1993, final rule.

D. The Proposal

FDA has tentatively concluded, based on the totality of publicly available evidence, that there is not significant scientific agreement that zinc supplementation will improve immune function in the elderly. Although it is well accepted that adequate dietary zinc is essential for normal immune function, a specific protective role of zinc supplementation of the elderly population has not been demonstrated. In fact, as discussed above, there is some evidence in recent well-controlled studies that high levels of zinc intake will suppress the immune function. FDA has not been presented with any evidence in the wake of its January 6, 1993, final rule on zinc and immune function in the elderly that would lead the agency to a different conclusion. Therefore, FDA is proposing to not authorize a health claim on the relationship of zinc and immune function in the elderly in the labeling of dietary supplements.

Because a dietary supplement would contain only zinc, and there is no evidence that the zinc supplementation itself plays a specific protective role in the elderly population, FDA tentatively finds that an appropriate basis for proposing to authorize a claim on zinc and immune function in the elderly on dietary supplements does not exist (56 FR 60652 and 58 FR 2661).

VI. Omega-3 Fatty Acids and Coronary Heart Disease

A. 1991 Proposed Findings

In the *Federal Register* of November 27, 1991 (56 FR 60663), FDA published a proposal on the use of a health claim regarding the relationship of *omega*-3 fatty acids and CHD. After reviewing the publicly available scientific evidence, the agency tentatively found that the evidence did not provide a basis to authorize a health claim on the label or in the labeling of foods. Examination of the epidemiological research on this topic revealed that the available studies applied only to the consumption of fish, which contain *omega*-3 fatty acids, and that it was not possible to ascribe any effects specifically to *omega*-3 fatty acids.

In deciding whether to authorize a health claim relating *omega*-3 fatty acids and CHD, FDA considered publicly available scientific evidence on the

public health significance of CHD, information on the properties of *omega*-3 fatty acids (56 FR 60663 at 60664), and comments that it had received on this topic (56 FR 60663 at 60665 and 60666). FDA reviewed consensus documents like the "Surgeon General's Report on Nutrition and Health," the National Academy of Science's "Diet and Health: Implications for Reducing Chronic Disease Risk" (56 FR 60663 at 60666), and other reports in the scientific literature, including epidemiological studies, animal studies, and other relevant information (56 FR 60663 at 60667 through 60671 and 60673 through 60676).

FDA tentatively determined that the publicly available evidence was not adequate to show that increased consumption of *omega*-3 fatty acids reduced the risk of CHD, particularly noting its lack of effect on serum cholesterol levels. FDA found that an increase in bleeding times and a decrease in platelet aggregation (which also may be associated with bleeding tendencies) had been observed consistently in normal healthy individuals, as well as in diseased persons, who consumed fish oils. The agency stated, however, that direct relationships between these effects and risk of CHD have not been established (56 FR 60663 at 60671).

The agency noted that *omega*-3 fatty acids had been shown to reduce blood pressure in hypertensive people to a small degree, which may bear on a relationship between *omega*-3 fatty acids and CHD. It stated that the effect was not of large magnitude (56 FR 60663 at 60672). Moreover, the agency also said that it had not been established that *omega*-3 fatty acids reduce blood pressure in normal subjects, and that it had not been demonstrated that the magnitude and duration of changes in blood pressure observed in short-term studies would persist during long-term consumption of *omega*-3 fatty acids. Finally, the agency noted the possibility that *omega*-3 fatty acids could increase the risk of CHD, through increases in LDL-cholesterol or apo- β -lipoprotein, among diabetics and hyperglycemics, and that *omega*-3 fatty acids might worsen control of blood glucose in diabetics. It said that these were significant safety concerns (56 FR 60663 at 60672). Given the lack of evidence that *omega*-3 fatty acids themselves reduced the risk of heart disease, specifically their lack of demonstrated effect on serum cholesterol (including LDL-cholesterol), the uncertainties about the relevance and significance of the blood pressure findings to the general populations, and the unresolved

safety concerns, the agency tentatively concluded not to authorize a health claim for *omega*-3 fatty acids and heart disease.

B. The January 1993 Final Rule

In the *Federal Register* of January 6, 1993 (58 FR 2682), FDA published a final rule that announced its decision not to authorize the use of a health claim regarding the relationship of *omega*-3 fatty acids and CHD on the label and in the labeling of foods in conventional food form.

FDA concluded that the totality of the available scientific evidence did not provide an adequate basis for a health claim. The agency said that the association between fish consumption and reduced risk of heart disease was not sufficient to establish a role for *omega*-3 fatty acids per se, versus other factors associated with dietary patterns high in fish, in achieving the desired effect. The agency noted that there was not significant scientific agreement that the physiological changes, such as increased bleeding times and a decrease in platelet aggregation, that were seen with consumption of *omega*-3 fatty acids would reduce the risk of CHD. The agency also said that the data were ambiguous because some effects of *omega*-3 fatty acids were not consistently observed, which suggested that other variables are important in determining whether an effect is seen (58 FR 2682 at 2702).

In the final rule, FDA also discussed some matters with respect to which greater agreement would be needed that the effects produced by *omega*-3 fatty acids are directly related to the risk of CHD before the agency could consider authorizing a claim. For example, many surrogate markers had been hypothesized, on the basis of limited evidence, to be related to specific diseases, including CHD, but few withstood the continued scrutiny of scientific investigation. FDA said that it could authorize a health claim only when there was significant scientific agreement, based on the totality of the scientific evidence, that a surrogate marker for a disease was a valid predictor of disease risk, specifically of heart disease risk for the general population. FDA said that evidence of such acceptance could be provided by a statement by an unbiased, nationally representative authoritative scientific or medical body (58 FR 2682 at 2705).

The agency reviewed numerous authoritative documents, the extensive comments that it had received on the proposal (58 FR 2682 at 2683 through 2699), and new scientific data, including epidemiological studies and

animal studies (58 FR 2682 at 2699 through 2705 and 2707 through 2714). Based on its review of all available information, the agency concluded that there are numerous physiological effects (e.g., increased bleeding times) of consumption of *omega*-3 fatty acids, but that at present, these endpoints are not generally accepted as being closely related to the risk of CHD. Thus the agency said that more data would be needed to show that the association between fish consumption and reduced risk of heart disease is specifically attributable to the *omega*-3 fatty acids in the fish.

The full discussion from the proposed and final rules, including the studies cited in those documents, is referenced herein.

C. Summary of Comments

In response to the January 6, 1993 final rule, the agency received two comments requesting that FDA allow voluntary inclusion of *omega*-3 fatty acid content information on food labels. These comments are not relevant to the issue of whether the agency can authorize a health claim on the relationship of *omega*-3 fatty acids and CHD. Therefore, no action on these comments is appropriate in this document. The agency points out, however, that in the *Federal Register* of June 18, 1993 (58 FR 33731 at 33736), it stated that under § 101.13(i)(3), information about the amount of a vitamin or mineral for which an RDI has not been established (e.g., vitamin K, selenium) could be declared on a food label, although not within the nutrition label, as long as the statement does not in anyway implicitly characterize the level of the nutrient and is not false or misleading in any respect. The agency notes that this provision would also apply to *omega*-3 fatty acid content information on food labels, including the labels of dietary supplements.

The agency did not receive any comments that provided any information that would support a health claim on the labels or in the labeling of dietary supplements regarding the relationship of *omega*-3 fatty acids and CHD in response to the January 6, 1993, final rule.

D. The Proposal

FDA has tentatively concluded, based on the totality of publicly available scientific evidence regarding the relationship of *omega*-3 fatty acids and coronary heart disease that there is not significant scientific agreement among experts that a claim about this relationship is scientifically valid.

There are numerous effects of *omega*-3 fatty acids that may be related to the risk of CHD, e.g., reduction in fasting and postprandial triglycerides, reductions in platelet aggregation and adhesion, and changes in the composition of lipoproteins. However, at this time, these endpoints are not generally recognized as being closely related to the risk of CHD.

Because a dietary supplement would contain only the *omega*-3 fatty acids, and there is not sufficient evidence that the *omega*-3 fatty acids alone caused the effects that were observed in studies of the effects of fish consumption on CHD, FDA tentatively finds that an appropriate basis for proposing to authorize a claim on *omega*-3 fatty acids and CHD on dietary supplements does not exist (56 FR 60663 and 58 FR 2682).

VII. The Next Steps

FDA has been diligent in developing proposed and final rules under the rigorous timeframes imposed by both the 1990 amendments and the DS Act of 1992. FDA has generally met its deadlines and is committed to completing the dietary supplement rulemakings in a timely manner. However, the agency has limited resources to both prepare the final rules that yet remain to be done under the 1990 amendments and the DS Act and to carry out the administrative activities required by the final rules under the 1990 amendments that the agency has already published. These activities include reviewing petitions, responding to inquiries, and conducting appropriate compliance activities, as well as preparing final rules in this and the five other rulemakings that are pending on dietary supplements.

The agency recognizes the emerging nature of the scientific information regarding the relationships between the intake of nutrients and disease or health-related conditions. A primary objective of FDA's administrative process is to provide a full airing of the scientific data and other relevant information on each of the nutrient-disease relationships listed in section 3 of the 1990 amendments.

FDA must consider both the validity of the link between the substance and the disease condition and the safety of the substance, especially when the purpose of the proposed health claim is to encourage intake of substance (in contrast to the claims on fat, for example, which encourage moderation in consumption). Care in reviewing safety is especially important when the claim is made for a substance in a dietary supplement because consumption of dietary supplements, in

contrast to most foods in conventional food form, is not self-limiting.

The process that FDA has engaged in with respect to folic acid and neural tube defects is an example of the agency's commitment to examine thoroughly all questions regarding a possible health claim. Initially, there was promising scientific evidence regarding a link between folic acid and the incidence of neural tube defects. However, there were also substantive safety questions in January 1993 that required further scrutiny and left the agency unable to authorize a health claim. Nevertheless, the agency did not abandon the issue but continued to address the issues by working with an expert advisory committee. Now, the agency is proposing to authorize a health claim on this nutrient-disease relationship.

The results of the rulemaking process for the five nutrient-disease relationships that the agency is initiating in this *Federal Register* document may differ. The agency may find that there is significant scientific agreement based on the totality of evidence for some of the relationships and may conclude that for other relationships, there is not such agreement. On still others, the agency may find that while evidence is promising, there are questions and concerns that must be resolved before a claim can be authorized. The agency will authorize a health claim in the first type of situation and will deny a health claim in the second type. With respect to the third type, the agency will also deny the health claim but will continue its process with respect to the relationship, with a goal of ensuring that interested persons obtain useful information that is scientifically valid and that will, in fact, be beneficial to health.

VIII. FDA's Plan for Completing a Final Rule

This proposal provides an opportunity for interested persons to submit new scientific data and comments in the five nutrient-disease relationships that are the subject of this rulemaking. The agency will review all comments received and will conduct its own literature review to obtain recent scientific evidence. In addition, FDA plans to cosponsor, with other research and health organizations, an open symposium on antioxidant vitamins to discuss the available science, to identify any unmet research needs, and to discuss ways of facilitating research to meet these needs. FDA will consider the results of this symposium in deciding whether to authorize a health claim on

antioxidant vitamins and cancer. FDA will provide notice of the meeting in the *Federal Register*. The agency intends to publish a final rule on this rulemaking in December of 1993, in accordance with the amendments to the 1990 amendments in the DS Act.

IX. Comments

Given the public health significance of cancer, CVD, and immune function in the elderly, FDA wants to make sure that its decisions in this proceeding reflect the latest scientific information. Therefore, FDA is requesting comments on any new data that have become available on the matters discussed in this document.

Interested persons may, on or before December 13, 1993, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between Monday through Friday.

X. Economic Impact

FDA has examined the economic implications of the proposed rule amending 21 CFR as required by the Regulatory Flexibility Act and Executive Order 12291. The Regulatory Flexibility Act requires regulatory relief for small businesses where feasible. Executive Order 12291 compels agencies to use cost-benefit analysis as a component of decisionmaking. The agency finds that this proposed rule does not constitute a major rule as defined by Executive Order 12291. In accordance with the Regulatory Flexibility Act, FDA has explored whether these proposed rules will have a significant impact on small businesses and has tentatively concluded that they do not.

In the *Federal Register* of November 27, 1991 (56 FR 60366), FDA published a number of proposed food labeling regulations to implement the provisions of the 1990 amendments (Pub. L. 101-535). The agency also published a regulatory impact analysis which preliminarily estimated the costs and benefits of the various proposed regulations and on which FDA asked for comments.

Final regulations that implemented the 1990 amendments, except with respect to dietary supplements, were issued on January 6, 1993, including a final regulatory impact analysis (RIA) of those final regulations (58 FR 2927). In the RIA, FDA responded to the

comments regarding dietary supplements with tentative conclusions.

As described previously in this preamble, FDA is proposing to amend its food labeling regulations to state that health claims regarding the five nutrient-disease relationships are not authorized for dietary supplements. There are several different types of products which may be considered to be dietary supplements. These products include dietary supplements of vitamins, minerals, herbs, and other similar nutritional substances. In the proposals of June 18, 1993, FDA estimated that there are about 5,000 vitamin, mineral, and other dietary supplement products marketed in the United States and approximately 15,000 labels.

There are two potential costs of this regulation if implemented as proposed: Relabeling costs for those products using unauthorized health claims which must be removed from labels or labeling and the inability to market certain products based on those health claims.

The agency estimates that very few, if any, products are currently using the health claims that the agency is proposing not to authorize. Therefore, FDA does not believe that this proposed rule will not result in any significant changes in labeling. Accordingly, this regulation would result in few costs or benefits.

XI. 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.

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, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 is revised 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, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355, 371); sec. 202(a)(2) of the Dietary Supplement Act (Pub. L. 102-571).

2. Section 101.71 is amended by revising the introductory text of paragraph (a) to read as follows:

§ 101.71 Health claims: claims not authorized.

(a) Health claims not authorized for foods in conventional food form or for dietary supplements of vitamins, minerals, herbs, or other similar substances:

Dated: October 1, 1993.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 93-25029 Filed 10-7-93; 2:51 pm]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 136, 137, and 139

[Docket No. 91N-100S]

Food Standards: Amendment of the Standards of Identity for Enriched Grain Products to Require Addition of Folic Acid

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the standards of identity for enriched bread, rolls and buns, enriched flour, enriched self-rising flour, enriched corn grits, enriched corn meals, enriched farina, enriched rice, enriched macaroni products, enriched nonfat milk macaroni, and enriched noodle products, and, by cross-reference, the standards of identity for enriched bromated flour, enriched vegetable macaroni products, and enriched vegetable noodle products, to require the addition of folic acid. The agency is proposing to require that these products be fortified with folic acid at levels ranging from 0.43 milligrams (mg) to 1.4 mg per pound (mg/lb) or 95 micrograms (μ g) to 309 μ g/100 grams (g) of product. These values are based on a fortification level of 140 μ g/100 g (0.635 mg/lb) of the cereal-grain product. This action is proposed on FDA's own initiative. It is intended in part to help women of childbearing age comply with the recommendation by the U.S. Public Health Service (PHS) that they consume at least 0.4 mg (400 μ g) daily of folate. This action also responds to a citizen petition submitted by Glenn Scott.

DATES: Written comments by December 13, 1993. The agency is proposing that any final rule that may issue, based on

this proposal, become effective 1 year after date of publication in the *Federal Register*.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Felicia B. Satchell, Center for Food Safety and Applied Nutrition (HFS-158), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-205-5099.

SUPPLEMENTARY INFORMATION:

I. Background

In September 1992, following an open meeting sponsored by the Centers for Disease Control (CDC) in Atlanta, GA (57 FR 29323) and based on reviews of the relevant scientific data, PHS recommended that all women of childbearing age in the United States consume 0.4 mg (400 µg) of folate daily to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects (Ref. 1). In discussing this recommendation, PHS raised several issues that directly bear on FDA's responsibilities under the Federal Food, Drug, and Cosmetic Act (the act). One of these issues was to identify the best approach for increasing intake of folate by women during their childbearing years. PHS identified several possible approaches by which folate intake by the target population might be increased. These approaches included: (1) Improvement of dietary habits, (2) fortification of the U.S. food supply, and (3) daily use of folate supplements by women throughout their childbearing years. The PHS recommendation also cautioned against the effects of higher intakes of folate. The recommendation stated that a widely recognized adverse effect of high intakes of folate is masking the anemia of vitamin B₁₂ deficiency and thus allowing the neurologic damage to progress untreated. PHS said that care should be taken to keep total folate consumption at less than 1 mg (1,000 µg)/day, except under the supervision of a physician (Ref. 1).

After the PHS recommendation was issued, FDA convened a subcommittee on folate of its Food Advisory Committee (hereinafter referred to as the "Folic Acid Subcommittee") to consider some of the issues raised by the recommendation. At a meeting in November 1992, the Folic Acid Subcommittee discussed approaches for ensuring that the folate intakes of women would be increased. It identified several approaches. These included: (1)

Development of a fortification scheme such that 90 percent of women of childbearing age could receive at least 400 µg of folate per day from all sources, while preventing excessively high folate intakes by nontarget groups; (2) appropriate labeling of foods, including dietary supplements; and (3) implementation of an educational program directed primarily at women of childbearing age that emphasizes the importance of folate intake before, during, and after conception and its effect on the incidence of neural tube defects. The Folic Acid Subcommittee also recommended that a surveillance and monitoring system be established to provide baseline data on vitamin B₁₂ status in subgroups of the population that might potentially be at greatest risk as a result of increased intakes of folate.

These issues and the Folic Acid Subcommittee's recommendations are fully discussed elsewhere in this issue of the *Federal Register* in a proposed rule entitled "Food Labeling; Health Claims and Label Statements: Folic Acid and Neural Tube Defects" (hereinafter referred to as the health claims proposal).

II. The Proposal

In this document, the agency is proposing to implement its tentative conclusion, discussed at length in the health claims proposal, that food fortification should be limited to cereal-grain products. Specifically, FDA is proposing to establish a fortification scheme that will assist women in the target population in increasing their daily intake of folate. This document also responds to a citizen petition (Docket No. 92P-0132), submitted by Glenn Scott, that requested that the agency amend the standards of identity for enriched cereal-grain products to include a requirement for the addition of folic acid, although the levels of addition suggested by the petitioner were lower than those that FDA is proposing to require in this document.

FDA is proposing to amend the following standards of identity to require the addition of folic acid: Enriched bread, rolls and buns (§ 136.115 (21 CFR 136.115)); enriched flour (§ 137.165 (21 CFR 137.165)); enriched self-rising flour (§ 137.185 (21 CFR 137.185)); enriched corn grits (§ 137.235 (21 CFR 137.235)); enriched corn meals (§ 137.260 (21 CFR 137.260)); enriched farina (§ 137.305 (21 CFR 137.305)); enriched rice (§ 137.350 (21 CFR 137.350)); enriched macaroni products (§ 139.115 (21 CFR 139.115)); enriched nonfat milk macaroni products (§ 139.122 (21 CFR 139.122)); and enriched noodle products (§ 139.155 (21

CFR 139.155)). FDA notes that the standards of identity for enriched bromated flour (§ 137.160 (21 CFR 137.160)), enriched vegetable macaroni products (§ 139.135 (21 CFR 139.135)), and enriched vegetable noodle products (§ 139.165 (21 CFR 139.165)) cross-reference the standards of identity for enriched flour, enriched macaroni products, and enriched noodle products, respectively, and will thus also be amended by this proposal. FDA also points out that the standard for enriched macaroni products fortified with protein is stayed and thus will not be addressed in this rulemaking.

As fully discussed in the health claims proposal published elsewhere in this issue of the *Federal Register*, FDA has tentatively decided that the fortification of the food supply is an appropriate approach for increasing the intake of folate by women in the target population. As noted by the Folic Acid Subcommittee and expert speakers who testified before the Folic Acid Subcommittee, food fortification has the advantage of reaching a great number of women in the target population before conception and during early pregnancy, when the risk of neural tube defects is greatest. It also has the advantage of providing folate in a continuous and passive manner and, thus, represents an effective means for improving the folate nutrition of women in their childbearing years.

In determining what foods would be appropriate for fortification with folic acid and at what levels, the agency used the U.S. Department of Agriculture (USDA) 1987-1988 national food consumption data (Ref. 2) to estimate daily intake of folate for the target population, as well as the general population, with fortification at different levels for cereal grains, dairy products, and juices. The agency estimated the effects of fortification using three values—0.070, 0.140, and 0.350 mg of folic acid/100 g of cereal-grain products. As discussed in the health claims proposal, the value of 0.070 mg/100 g (0.3 mg/lb) is the amount, recommended in 1974 by the Food and Nutrition Board, National Research Council, National Academy of Sciences, that would restore folate lost in the milling of cereal-grain products and represents about a four-fold increase in the level of folate that ordinarily occurs in wheat flour (Ref. 3). The value of 0.140 mg/100 g is twice that amount, and 0.350 mg/100 g is five times that amount.

The different approaches that FDA used in estimating the effects of fortification of food with these levels of folic acid are fully discussed in the

health claims proposal, published elsewhere in this issue of the *Federal Register*. In arriving at these estimates, FDA made provision for consumption of ready-to-eat cereals fortified with folic acid as well as dietary supplements containing folic acid.

In its analysis, FDA assumed likely underreporting biases in food intakes. The agency did so because national food consumption surveys generally underestimate the food intake of survey respondents. This fact is supported, in part, by the observation that when consumer-reported dietary intakes are used as a basis for designing intervention diets (not necessarily for weight reduction), subjects that follow the intervention diet frequently lose weight (Ref. 4). Further, calorie intakes that were estimated based on the survey respondents' daily reported food intake fell below the current average calorie intakes recommended by the Food and Nutrition Board. For example, in the 1987-1988 USDA Nationwide Food Consumption Survey (Ref. 2) used for these estimates, calculated median energy intakes of women 19 to 50 years of age were only about 1,500 calories, whereas the most recent recommended average energy intake for this gender/age group is 2,200 calories (Ref. 5).

FDA also took into account in performing its analysis that underestimation of folate contents of foods was likely in the analysis that had been done. Comparison of newer methods of sample preparation with older methods for determining the folate content of foods has revealed underestimates in the range of 20 percent for vegetables such as spinach and cauliflower and 50 percent for canned tuna. Thus, commonly used methods for folate analysis may significantly underestimate the folate content of foods.

As fully discussed in the health claims proposal published elsewhere in this issue of the *Federal Register*, results of FDA's analysis show that when fortification included fruit juices and dairy products in addition to cereal grain and dietary supplements, folate intakes of some nontarget group consumers exceeded 1 mg/day regardless of the fortification level examined. However, when fortification was limited to cereal-grain products at levels of 70 µg/100 g or 140 µg/100 g, daily intake levels remained below 1 mg/100 g. At fortification levels of 350 µg/100 g, the estimated daily intake could reach levels of 1,220 µg/100 g, which exceeds the recommended safe upper limit.

The agency also estimated the daily intake of folate for consumers who

follow Federal government dietary guidance, such as the U.S. Dietary Guidelines and the Department of Health and Human Services (DHHS)/USDA Food Guide Pyramid, and consume cereal-grain products fortified with folic acid, to determine whether these consumers will have daily intakes in excess of the recommended safe upper limit of approximately 1 mg/day.

These estimates, as shown in Table 7 in the health claims proposal, indicate that consumers who followed even the low end of recommendations from the DHHS/USDA Food Guide Pyramid could, without supplement use, easily consume 420 µg or more of folate per day from cereal-grain products fortified with 70 µg folic acid/100 g. Further, such consumers' daily intake could triple if such products were fortified with 350 µg folic acid/100 g.

As a result of its analysis of fortification of several cereal-grain, dairy, and juice products, FDA has tentatively concluded that fortification should be limited to cereal-grain products and not extended to dairy products and fruit juices. (The agency notes that results of its analysis are presented in Tables 4 through 7 in the health claims proposal published elsewhere in this issue of the *Federal Register*.) The agency found that intakes by very large segments of the general population would reach several milligrams per day if all of these foods were fortified with folic acid.

The agency has also tentatively decided that the appropriate fortification level for cereal-grain products is 140 µg/100 g. Based on the results of its analysis, fortification of cereal-grain products with 140 µg/100 g will provide daily intakes for the nontarget population that remain within the recommended safe upper limit of approximately 1 mg/day, while providing increased intakes of folate for women in their childbearing years. The agency notes that with supplement use, 95th percentile intakes by adults 51+ years of age could reach 840 to 860 µg/day if these enriched cereal-grain products are fortified with 140 µg/100 g. While the agency recognizes that this level approaches the recommended safe upper limit and does not take into account likely underreporting biases regarding food intakes and underestimation of folate content of foods, it tentatively concludes that fortification of cereal-grain products with 140 µg/100 g folic acid is the most appropriate fortification level of the three levels analyzed to ensure that folate intakes by the target population will increase. Fortification at a lower level of 70 µg/100 g may not provide

sufficient folate levels to that portion of the target population that have lower daily food intakes or that consume minimal amounts of cereal-grain products. For example, folate intake estimates for the 25th percentile of the target population if cereal-grain products were supplemented with 70 µg/100 g of folic acid showed levels of 160 to 180 µg/day without supplement use and 200 µg/day with supplement use.

In this document, the agency is proposing to provide for folic acid fortification of the individual enriched cereal-grain products discussed below, which are subject to standards of identity.

A. Bakery and Wheat Flour Products

1. Enriched Flour

Wheat flour products are produced in various forms, plain, self-rising, instantized, and enriched. The products may be sold directly to consumers or may be specially designed for manufacturing bakery products, i.e., breads, rolls and buns, or other specialty food products. Standards of identity for enriched forms of these products provide for addition of specified amounts of thiamin, niacin, riboflavin, and iron and, in some instances, for the optional addition of calcium and vitamin D. (FDA is providing for correction of the spelling of "thiamin" in all the food standards that it is proposing to amend.)

As stated above, FDA has tentatively concluded that it is appropriate to fortify enriched cereal-grain products with folic acid based on a fortification level of 140 µg/100 g for wheat flour. This level will provide a better opportunity for a larger portion of the target population to achieve significantly increased folate intakes.

In determining what minimum level of folate should be present in enriched wheat flour, FDA consulted the Food and Nutrition Board's report of the proceedings of a workshop entitled "Technology of Fortification of Cereal-Grain Products" conducted in May 1974 (Ref. 6) and the USDA Handbook 8-20, *Composition of Foods: Cereal Grains and Pasta, Raw, Processed, Prepared* (Ref. 7). The Food and Nutrition Board's report included a paper by Kulp that provided information on naturally occurring levels of vitamins and minerals in commercially milled wheat flour. The paper reported summary data, collected by members of the industry, academia, and the governments of the United States and Canada, on the analysis of 65 samples of various types of flours originating from mills in the

United States and Canada. The average folate content of wheat flour was shown to be 0.076 mg/lb (or 0.017 mg/100 g), with a range of 0.044 to 0.120 mg/lb (or 0.009 to 0.026 mg/100 g).

The USDA Handbook 8-20 lists values for folate content (listed as folacin) of four types of wheat flour other than whole grain flour, i.e., all purpose, bread, cake, and self-rising wheat flours. The folate values for the flour products, in order of the foregoing list, are 0.117, 0.131, 0.086, and 0.191 mg/lb (or 0.026, 0.029, 0.019, and 0.042 mg/100 grams) (Ref. 7). These values are somewhat higher than the average value, 0.076 mg/lb (range 0.044 to 0.120 mg/lb), reported for wheat flour in the Food and Nutrition Board's report (Fig. 1, p.14, Ref. 6). However, the USDA Handbook 8-20 values for folate content in wheat (before milling) and whole wheat flour, ranging from 0.171 to 0.196 mg/lb (or 0.038 to 0.044 mg/100 g), were lower than the Food and Nutrition Board's recommended restoration level of 0.3 mg/lb folic acid for milled (i.e., bran removed) wheat flour products.

Given these data, FDA has tentatively decided to use the average normally occurring level for folate content in wheat flours cited in the Food and Nutrition Board's report because it is based on a more comprehensive data base on the folate content of wheat flour. The agency is not aware of subsequent studies of this nature that would alter the findings of this study. Thus, to fortify wheat flour at a level of 140 µg/100 g (0.635 mg/lb), FDA is proposing that enriched flour contain 0.7 mg/lb of folic acid. FDA derived this value by adding the proposed fortification level of 0.635 mg/lb to the Food and Nutrition Board's folate value for unfortified flour of 0.076 mg/lb, which yields 0.711 mg/lb, and rounding this value to 0.7 mg/lb. Accordingly, based on this calculation, FDA is proposing to amend the standards of identity for enriched flour (§ 137.165) and enriched self-rising flour (§ 137.185), and by cross-reference, enriched bromated flour (§ 137.160), to require that these foods contain 0.7 mg/lb of folic acid.

2. Enriched Rolls and Buns

For consistency with the requirements for enriched flour products, FDA is proposing to amend the standards of identity for enriched bread, rolls, and buns in § 136.115 to require that these foods contain 0.43 mg/lb of folic acid. This rate of fortification is proportionally consistent with the fortification rate used for the B vitamins (thiamin, riboflavin, and niacin) when enriched flour is used in making these

foods. For example, the levels of thiamin, riboflavin, and niacin in enriched flour (§ 137.165) are 2.9, 1.8, and 24.0 mg/lb, respectively, and in enriched bread (§ 136.115) are 1.8, 1.1, and 15.0 mg/lb, resulting in a ratio of approximately 1.62 to 1. In the case of the level of folic acid, the proposed level for enriched flour is 0.7 mg/lb compared to 0.43 mg/lb for bread, resulting in a ratio 1.63 to 1. The lower level specified for the B vitamins and folic acid content in enriched bread products allows the bread products to be made from the standardized enriched flour without further fortification.

3. Enriched Farina

FDA is also proposing a fortification level for folic acid in enriched farina (§ 137.305) on the same basis as that for enriched wheat flour, i.e., 1 lb of the food would contain not less than 0.7 mg of folic acid. Both wheat flour and farina are made from the endosperm of wheat, that portion of the wheat kernel that remains after the bran layer and germ have been removed. The bran layer and germ contain most of the B vitamins, including the naturally occurring folate. Therefore, the agency tentatively finds that it is reasonable to fortify both flour and farina at the same level of 140 µg/100 g or 0.7 mg/lb.

FDA notes that, like flour, farina is not consumed directly but is prepared in some recipe. The enriched farina may be rinsed before use and is usually boiled in water. These steps are likely to dilute the levels of nutrients in the food. Because of such possible losses, the agency is also proposing an upper limit of addition (0.87 mg/lb). The upper limit for folic acid is approximately 25 percent higher to counter possible losses of the vitamin in preparation of the finished food product and is consistent with the upper levels of other B vitamins in the standard.

B. Corn and Rice Products

1. Enriched Corn Grits

USDA Handbook 8-20 data (Ref. 7) show that corn products, except for corn meals, contain significantly less folate than wheat products, ranging from a low of 0.005 mg/100 g (0.022 mg/lb) in dry corn grits to a high of 0.031 mg/100 g (0.141 mg/lb) in degermed corn meals and 0.057 mg/100 g (0.258 mg/lb) in bolted corn meals. However, because corn products are often used as substitutes for wheat based food products, FDA is proposing to amend § 137.235 to require fortification of enriched corn grits with the same level of folic acid as that proposed for enriched wheat flour products, such

that each pound of the food would contain at least 0.7 mg of folic acid. Because there may be losses from the rinsing of corn grits before cooking, FDA is also proposing an upper limit for folic acid fortification of 1.0 mg/lb, which is approximately 50 percent higher than the proposed minimum of 0.7 mg/lb, as it has done for the other B vitamins (thiamin, riboflavin, and niacin) that are required to be present in enriched corn grits.

2. Enriched Corn Meals

In the case of enriched corn meals under § 137.260, FDA is proposing a minimum folic acid level that is consistent with that for enriched flour, such that each pound of the food contains 0.7 mg. As noted above, corn products may be used as substitutes for wheat products. Thus, FDA believes that consumers expect to be able to obtain the same levels of nutrients from enriched corn meals as from enriched wheat flour. FDA is also proposing an upper limit for folic acid addition (i.e., 1.0 mg/lb which is approximately 50 percent higher than the minimum fortification level), as it has done for the added B vitamins. The upper limit on the other B vitamins is intended to prohibit addition of excessive amounts of the nutrient and to ensure uniformity in composition of corn meals. FDA tentatively finds that for the same reasons an upper limit on the addition of folic acid of 1.0 mg/lb is necessary.

3. Enriched Rice

The folic acid content of rice varies from 0.008 mg/100 g (0.036 mg/lb) for white rice to 0.020 mg/100 g (0.090 mg/lb) for brown rice (Ref. 7). FDA is proposing to amend the standard of identity for enriched rice (§ 137.350) to include a range for the folic acid fortification level, 0.7 mg/lb to 1.4 mg/lb, with the lower limit being consistent with the proposed folic acid fortification level for enriched wheat flour. FDA believes that use of the same minimum level of fortification is appropriate because it is consistent with the Food and Nutrition Board's recommendation that the same restoration level be used for wheat flour, corn products, and rice. However, as discussed above, FDA believes a level (0.635 mg/lb) that is approximately twice that of the Food and Nutrition Board's recommended level (0.3 mg/lb) is necessary to ensure that sufficient levels of folate are available to meet the dietary needs of the target population.

FDA is also proposing that the upper limit for folic acid fortification of enriched rice be twice the proposed minimum fortification level for folic

acid (0.7 mg/lb) or 1.4 mg/lb, as it has done with other added nutrients in enriched rice. This proposed upper level is based on the way that rice is fortified in this country.

In the United States rice may be enriched by addition of a powder mixture containing the added nutrients or by use of a rice premix consisting of rice kernels coated with a concentrated nutrient mix. When the powder enrichment procedure is used, the label of the package is required to state that the rice should not be rinsed before cooking or drained after cooking, so that the rice retains the added nutrients. However, there is no assurance that these instructions will be followed. In the case of the rice premix, a special coating is applied to the rice kernels, so that the added nutrients will not be washed off if the product is rinsed before cooking. The coated rice premix is blended with unenriched rice such that the finished enriched rice product will contain the required minimum levels of added nutrients. The stated range provides flexibility in the production of the enriched rice and ensures that the food, when prepared for consumption, will contain the required minimum levels of nutrients.

The agency believes that most, if not all, enriched rice is manufactured using a rice premix procedure, and that it may not be necessary to continue to provide for the range of added nutrients in the standard of identity for enriched rice (Ref. 8). If comments provide substantive information that enriched rice is generally being prepared in this manner, or that the specified level of added nutrients is maintained during cooking when the rice is prepared according to labeled instructions on the package, FDA will consider not including the upper limit of the proposed range, and establishing a single level for folic acid addition (0.7 mg/lb), in any final rule that is published in this proceeding.

C. Macaroni and Noodle Products

The standards of identity for enriched macaroni products (§ 139.115), enriched nonfat milk macaroni (§ 139.122), and enriched noodle products (§ 139.155), and the cross-referenced standards of identity for enriched vegetable macaroni products (§ 139.135) and enriched vegetable noodle products (§ 139.165), provide for significantly higher levels of nutrient addition than the related flour standards of identity because these products are usually cooked in a large amount of water that is usually discarded after cooking and before consumption of the macaroni and noodle products. FDA is proposing to

require addition of folic acid to macaroni and noodle products in the same proportion as it is proposing for use in enriched flour, except that the proposed level (expressed in terms of a range) will be approximately 25 percent higher than the proposed level of folic acid to be added to flour. This 25 percent increase is consistent with that of the other added nutrients (thiamin, riboflavin, niacin, and iron) in the enriched macaroni and noodle products standards compared to those in the standards of identity for flour products. Accordingly, FDA is proposing to require that the enriched macaroni and noodle products contain from 0.9 to 1.2 mg/lb of folic acid.

The agency requests comments on whether the proposed fortification levels discussed for the above products are appropriate. Interested persons who wish to suggest alternative fortification levels should include a rationale for such levels and data to support the suggested levels. Further, the agency requests comments on whether addition of folic acid to these cereal-grain products should be required as proposed or should be optional because increased levels of folate intake present health risks to persons with vitamin B₁₂ deficiency.

Minor editorial changes have been made in the standards of identity to achieve consistency in language format.

III. Economic Impact

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act and Executive Order 12291. The Regulatory Flexibility Act requires relief for small businesses where feasible. Executive Order 12291 compels agencies to use cost-benefit analysis as a component of decisionmaking. The agency finds that this proposed rule is not a major rule as defined by Executive Order 12291. In accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612), FDA has also determined that this proposed rule will not have a significant adverse impact on a substantial number of small businesses.

A. Options

FDA has evaluated the following options: (1) Improve dietary practices among women of childbearing age to increase their daily folate intake, (2) change the standards of identity to require fortification of cereal-grain products with folic acid at levels of 0.14 mg of folate per 100 g of cereal-grain product, and (3) change the standards of identity to require fortification of cereal-grain products with folic acid at either 0.07 mg/100 g or 0.35 mg/100 g.

B. Costs

1. Improve Dietary Practices Among Women of Childbearing Age

Under this option, Federal and State health agencies would encourage improved dietary practices among women of childbearing age to increase their daily folate intake. This might be accomplished under any of the numerous existing programs, through government outreach programs, and physicians. This option will work in conjunction with health claims which are expected to increase the intake of folate by women of childbearing age. However, the agency is unsure of the potential cost or efficacy of this option and requests comments on it.

2. Require Fortification with Folic Acid at 0.14 mg/100 g

Excess folate intake can interfere with the diagnoses of vitamin B₁₂ deficiency at levels as low as 0.25 mg per day. There is no scientific consensus on the percentage of diagnoses of vitamin B₁₂ deficiency that would be complicated by folate intake at this level. However, the agency has tentatively determined that adverse health effects are not significant until folate intake reaches 1 mg per day. Under this option, folate intake will be below 1 mg per day for all individuals.

The cost of the folic acid that must be added to the specified cereal-grain products is estimated to be approximately \$4 million per year. The cost of analytical testing depends on how many tests are run. As an example of the costs involved, if each affected manufacturing plant tests five products for folic acid content three times per year, total testing costs would be \$2.5 million per year. The cost of required label changes is estimated to be about \$20 million.

In addition, some countries, including Canada, do not allow folic acid fortification of these products. Thus, this option would require that separate production runs be made for fortified products exported to and imported from these countries. FDA cannot estimate these costs at this time.

The total cost of this option is estimated to be \$27 million per year plus the cost of separate production runs for these products exported to and imported from certain foreign countries.

3. Require Fortification with Folic Acid at 0.07 mg/100 g or at 0.35 mg/100 g

Folic acid fortification at 0.07 mg/100 g will not raise the folate intake of consumers at risk of vitamin B₁₂ deficiency and pernicious anemia to levels greater than 1 mg per day. The

cost of the required folic acid is approximately \$2 million per year. The cost of testing is estimated to be about \$2.5 million per year and the cost of the required label changes \$20 million. Total costs of folic acid fortification at 0.07 mg/100 g are therefore estimated to be \$25 million.

Folic acid fortification at 0.35 mg/100 g will raise the folate intake of some consumers at risk of vitamin B₁₂ deficiency and pernicious anemia to levels exceeding 1 mg per day. As an example of the costs involved, a simple linear extrapolation of the results of a study that found that between 50 percent and 77 percent of patients with pernicious anemia experienced prolonged hematological remission to a dose of 5 mg of folate per day will be used (Ref. 9).

A delay in the diagnosis of vitamin deficiency can result in severe and potentially irreversible neurologic damage. The most common irreversible consequences of a delay in the diagnosis of vitamin B₁₂ deficiency are permanent paresthesia (numbness or tingling) in the hands or feet and ataxia (inability to coordinate voluntary muscular movements). Based on the number of people estimated to be at risk of pernicious anemia, and on a study dealing with the prevalence of permanent paresthesia and ataxia in cases of pernicious anemia initially diagnosed at the stage at which neurologic symptoms are present, consumers may experience health consequences valued at approximately \$1.85 billion per year under this level of folic acid fortification (Ref. 10).

The cost of the folic acid required to obtain 0.35 mg/100 g is approximately \$10 million per year. The cost of testing is estimated to be \$2.5 million and the cost of the required label changes \$20 million.

Total costs of folic acid fortification at 0.35 mg/100 g are therefore estimated to be \$1.88 billion per year plus the cost of separate production runs for these products exported to and imported from certain foreign countries.

C. Benefits

1. Improve Dietary Practices Among Women of Childbearing Age

As indicated above, the agency cannot estimate the benefit of this option at this time. FDA requests comments on the benefits of this option.

2. Require Fortification with Folic Acid at 0.14 mg/100 g.

The benefit of this option is a reduction in the incidence of infants born with neural tube defects (NTD's).

PHS has estimated that if all women of childbearing age achieved an intake of 0.4 mg folate per day the incidence of NTD's could be reduced by 50 percent.

The agency is proposing elsewhere in this issue of the *Federal Register* to allow health claims for folic acid. In order to determine the number of women whose folate intake will exceed 0.4 mg per day due to the proposed level of folic acid fortification, the increase in folate consumption due to health claims must be estimated. FDA has insufficient information to estimate the increase in folate intake due to health claims alone. As an example of the benefits involved, the following assumes that all women currently taking dietary supplements will take supplements containing 0.4 mg folic acid per day once health claims for folic acid are allowed.

NTD's are rare but serious birth defects that can result in infant mortality or serious disability. There are about 2,500 cases of NTD's each year. Based on a linear extrapolation of the PHS estimate cited above and the percentage of women whose folate intake would exceed 0.4 mg per day due to folic acid fortification at 0.14 mg/100 g, this option is estimated to eliminate about 116 NTD's each year. In 1989, NTD's accounted for 533 infant deaths. If this figure is representative, this option should prevent about 25 infant deaths each year.

There is no consensus on the value of a reduction in risk corresponding to one statistical infant life saved. If the value of a statistical life saved does not vary with life years remaining, a reasonable estimate is \$5 million. If the value of a statistical life saved does vary with life years remaining, a reasonable estimate is \$11 million (Ref. 11). The value of the infant deaths avoided each year is therefore estimated to be between \$123 million and \$260 million.

The birth defects anencephaly and spina bifida are the most common forms of NTD's and account for about 90 percent of these defects. Spina bifida is a serious condition that is associated with a variety of adverse health effects. One study of the effects of spina bifida found that 41 percent of patients born with spina bifida died before their 16th birthday (Ref. 12). Assuming that the estimated number of infant deaths are due primarily to anencephaly, the increase in life expectancy due to the elimination of the estimated number of cases of spina bifida is estimated to be about \$323 million. This study also found that 20 percent of patients with spina bifida who did not die before their 16th birthday suffered from mental retardation, 30 percent were wheelchair

bound, and 44 percent incontinent (Ref. 12). The estimated benefit from the elimination of these adverse health effects is estimated to be \$205 million per year (Ref. 11). This estimate is based on a willingness-to-pay methodology that includes, for example, cost of illness and pain and suffering. Benefit estimates based solely on cost of illness would be significantly lower. Additional adverse health effects from NTD's were also observed but were relatively rare and will not be considered here.

Total benefits of this option are therefore estimated to be approximately \$651 to \$788 million per year.

3. Require Fortification with Folic Acid at 0.07 mg/100 g or at 0.35 mg/100g

Based on the methodology discussed above, the benefit of requiring fortification of these products at 0.07 mg/100 g is estimated to be between \$326 million and \$394 million.

Based on the methodology discussed above, the benefit of requiring fortification of these products at 0.35 mg/100 g is estimated to be between \$1.63 billion and \$1.97 billion. This option is the only option that would generate health costs.

D. Conclusion

In accordance with Executive Order 12291, the agency has analyzed the economic effects of this proposed rule and has determined that this rule, if promulgated, will not be a major rule as defined by that order.

The costs of the proposed action are estimated to be approximately \$27 million per year plus the cost of separate production runs for products exported to and imported from certain foreign countries. The benefits are estimated to be from \$651 to \$788 million per year.

IV. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Because the agency is proposing to take three actions involving folic acid and the net effect of these actions is likely to increase the usage of folic acid, one environmental assessment has been

prepared which considers all three agency actions.

V. 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.

1. CDC, "Recommendations for the Use of Folic Acid to Reduce the Number of Cases of Spina Bifida and Other Neural Tube Defects," *Morbidity and Mortality Weekly Reports*, 41, 1-7, 1992.

2. USDA, Nationwide Food Consumption Survey/Individual Intake—1987-1988, accession no. PB90-504044, National Technical Information Service, Springfield, VA, 1990.

3. Food and Nutrition Board, National Research Council, National Academy of Sciences, *Proposed Fortification Policy for Cereal-Grain Products*, 36 pp., National Academy of Sciences, Washington, DC, 1974.

4. Mertz, W., J. C. Tsui, J. T. Judd, and S. Reiser, et al., "What are People Really Eating? The Relation Between Energy Intake Derived From Estimated Diet Records and Intake Determined to Maintain Body Weight," *American Journal of Clinical Nutrition*, 54:291-295, 1991.

5. Food and Nutrition Board, National Research Council, National Academy of Sciences, "Recommended Dietary Allowances," 10th ed., Washington, DC, 1989.

6. Subcommittee on Food Technology, Committee on Food Protection, Food and Nutrition Board, National Research Council, National Academy of Sciences, Proceedings of a Workshop on Technology of Fortification of Cereal-Grain Products, Washington, DC, May 16-17, 1977.

7. USDA Handbook 8-20: Composition of Foods, Cereal Grains and Pasta, Raw Processed, Prepared. Rev., October 1989.

8. Hoffpauer, D.W., "Rice Enrichment for Today," *Cereal Foods World*, vol. 37, No. 10, pp. 757-759, 1992.

9. Schwartz, S. O., S. R., Kaplan, and B. E., Armstrong, "The Long-Term Evaluation of Folic Acid in the Treatment of Pernicious Anemia," *Journal of Laboratory and Clinical Medicine*, 35: 894-898, 1950.

10. Heaton, E. B., D. G. Savage, J. C. Brust, T. J. Garrett, J. Lindenbaum, "Neurologic Aspects of Cobalamin Deficiency," *Medicine*, vol. 7, No. 4, pp. 229-245, July 1991.

11. Research Triangle Institute, "Quality of Well-Being Scale in Estimating the Value of Consumers' Loss From Food Violating the FD&C Act," vol. II, Final Report, September 1988.

12. Hunt, G. M., "Open Spina Bifida: Outcome for a Complete Cohort Treated Unselectively and Followed Into Adulthood," *Developmental Medicine and Child Neurology*, vol. 32, No. 2, pp. 108-118, February 1990.

VI. Comments

Interested persons may, on or before December 13, 1993, submit to the Dockets Management Branch (address

above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy.

Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above, between 9 a.m. and 4 p.m., Monday through Friday.

During the comment period for this proposal, the agency intends to convene public meetings of the Folic Acid Subcommittee and the Food Advisory Committee for a discussion of the issues raised in this document, as well as the Health Claim document and the Standards of Identity document. FDA also intends to request comments from the experts who participated in its November 23 and 24, 1992, meeting of its Folic Acid Subcommittee. The agency will make any comments received from these experts and the views of the committees available for public review and comment immediately after the Advisory Committee meeting. In addition, FDA will endeavor to have copies of the transcripts of the Folic Acid Subcommittee and Food Advisory Committee meetings available as quickly as possible.

List of Subjects

21 CFR Part 136

Bakery products, Food grades and standards.

21 CFR Part 137

Cereals (food), Food grades and standards.

21 CFR Part 139

Food grades and standards.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs it is proposed that 21 CFR parts 136, 137, and 139 be amended as follows:

PART 136—BAKERY PRODUCTS

1. The authority citation for 21 CFR part 136 is revised to read as follows:

Authority: Secs. 201, 401, 403, 409, 701, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 343, 348, 371, 379e).

2. Section 136.115 is amended by revising paragraph (a)(1) to read as follows:

§ 136.115 Enriched bread, rolls, and buns.

(a) * * *

(1) Each such food contains in each pound 1.8 milligrams of thiamin, 1.1 milligrams of riboflavin, 15 milligrams

of niacin, 0.43 milligrams of folic acid, and 12.5 milligrams of iron.

* * * * *

PART 137—CEREAL FLOURS AND RELATED PRODUCTS

3. The authority citation for 21 CFR part 137 is revised to read as follows:

Authority: Secs. 201, 401, 403, 409, 701, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 343, 348, 371, 379e).

4. Section 137.165 is amended by revising paragraph (a) to read as follows:

§ 137.165 Enriched flour.

* * * * *

(a) It contains in each pound 2.9 milligrams of thiamin, 1.8 milligrams of riboflavin, 24 milligrams of niacin, 0.7 milligrams of folic acid, and 20 milligrams of iron.

* * * * *

5. Section 137.185 is amended by revising paragraph (a) to read as follows:

§ 137.185 Enriched self-rising flour.

* * * * *

(a) It contains in each pound 2.9 milligrams of thiamin, 1.8 milligrams of riboflavin, 24 milligrams of niacin, 0.7 milligrams of folic acid, and 22 milligrams of iron.

* * * * *

6. Section 137.235 is amended by revising paragraph (a)(1) to read as follows:

§ 137.235 Enriched corn grits.

(a) * * *

(1) It contains in each pound not less than 2.0 milligrams (mg) and not more than 3.0 mg of thiamin, not less than 1.2 mg and not more than 1.8 mg of riboflavin, not less than 16 mg and not more than 24 mg of niacin or niacinamide, not less than 0.7 mg and not more than 1.0 mg of folic acid, and not less than 13 mg and not more than 26 mg of iron (Fe).

* * * * *

7. Section 137.260 is amended by revising paragraph (a)(1) to read as follows:

§ 137.260 Enriched corn meals.

(a) * * *

(1) It contains in each pound not less than 2.0 milligrams (mg) and not more than 3.0 mg of thiamin, not less than 1.2 mg and not more than 1.8 mg of riboflavin, not less than 16 mg and not more than 24 mg of niacin or niacinamide, not less than 0.7 mg and not more than 1.0 mg of folic acid, and not less than 13 mg and not more than 26 mg of iron (Fe).

* * * * *

8. Section 137.305 is amended by revising paragraph (a)(1) to read as follows:

§ 137.305 Enriched farina.

(a) * * *

(1) It contains in each pound not less than 2.0 milligrams and not more than 2.5 milligrams of thiamin, not less than 1.2 milligrams and not more than 1.5 milligrams of riboflavin, not less than 16.0 milligrams and not more than 20.0 milligrams of niacin or niacinamide, not less than 0.7 milligrams and not more than 0.87 milligrams of folic acid, and not less than 13.0 milligrams of iron (Fe).

* * * * *

9. Section 137.350 is amended by revising paragraph (a)(1) to read as follows:

§ 137.350 Enriched rice.

(a) * * *

(1) Not less than 2.0 milligrams and not more than 4.0 milligrams of thiamin, not less than 1.2 milligrams and not more than 2.4 milligrams of riboflavin, not less than 16 milligrams and not more than 32 milligrams of niacin or niacinamide, not less than 0.7 milligrams and not more than 1.4 milligrams of folic acid, and not less than 13 milligrams and not more than 26 milligrams of iron (Fe).

* * * * *

PART 139—MACARONI AND NOODLE PRODUCTS

10. The authority citation for 21 CFR part 139 is revised to read as follows:

Authority: Secs. 201, 401, 403, 409, 701, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 343, 348, 371, 379e).

11. Section 139.115 is amended by revising paragraph (a)(1) to read as follows:

§ 139.115 Enriched macaroni products.

(a) * * *

(1) Each such food contains in each pound not less than 4.0 milligrams (mg) and not more than 5.0 mg of thiamin, not less than 1.7 mg and not more than 2.2 mg of riboflavin, not less than 27 mg and not more than 34 mg of niacin or niacinamide, not less than 0.9 mg and not more than 1.2 mg of folic acid, and not less than 13 mg and not more than 16 mg of iron (Fe);

* * * * *

12. Section 139.122 is amended by revising the first sentence of paragraph (a)(3) to read as follows:

§ 139.122 Enriched nonfat milk macaroni products.

(a) * * *

(3) Each such food contains in each pound not less than 4.0 milligrams and not more than 5.0 milligrams of thiamin, not less than 1.7 milligrams and not more than 2.2 milligrams of riboflavin, not less than 27 milligrams and not more than 34 milligrams of niacin or niacinamide, not less than 0.9 milligrams and not more than 1.2 milligrams of folic acid, and not less than 13 milligrams and not more than 16 milligrams of iron (Fe). * * *

13. Section 139.155 is amended by revising paragraph (a)(1) to read as follows:

§ 139.155 Enriched noodle products.

(a) * * *

(1) Each such food contains in each pound not less than 4 milligrams (mg) and not more than 5 mg of thiamin, not less than 1.7 mg and not more than 2.2 mg of riboflavin, not less than 27 mg and not more than 34 mg of niacin or niacinamide, not less than 0.9 mg and not more than 1.2 mg of folic acid, and not less than 13 mg and not more than 16.5 mg of iron (Fe);

* * * * *

Dated: September 13, 1993.
David A. Kessler,
Commissioner of Food and Drugs.
[FR Doc. 93-25030 Filed 10-7-93; 2:51 pm]
BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. 91N-100F]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Folic Acid (Folacin)

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the food additive regulations to set limitations for the use of folic acid on a per serving basis in accord with the Nutrition Labeling and Education Act of 1990 (the 1990 amendments); to allow for the addition of folic acid to foods for which standards of identity exist, where such standards permit the addition of folic acid; to restrict to breakfast cereals the foods, for which standards of identity do not exist, to which folic acid may be added; to continue to permit the use of folic acid in infant formulas, dietary supplements, and foods for special dietary use; and to incorporate specifications for folic acid consistent with those in the Food Chemicals Codex.

DATES: Written comments by December 13, 1993.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Dennis M. Keefe, Center for Food Safety and Applied Nutrition (HFS-206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-254-9523.
SUPPLEMENTARY INFORMATION:

I. Background

A. Introduction

The 1990 amendments to the Federal Food, Drug, and Cosmetic Act (the act) provide in section 403(r)(1)(B) (21 U.S.C. 343(r)(1)(B)) that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition (a "health-claim"), unless the claim is made in accordance with the procedures and standards established under the act. FDA published a final rule on general requirements for health claims on January 6, 1993 (58 FR 2478). The regulation provides that FDA will promulgate regulations authorizing health claims only when it determines, based on the totality of publicly available scientific evidence, that there is significant agreement, among experts qualified by training or experience to evaluate such claims, that the claim is supported by the scientific evidence.

The 1990 amendments required that FDA evaluate 10 nutrient-disease relationships with respect to their appropriateness for health claims; the topic of folic acid and neural tube defects was among those 10 topics. On November 27, 1991, the agency proposed (56 FR 60610) not to authorize the use of a health claim relating to an association between folic acid¹ and neural tube defects on the label or in labeling of foods, including dietary supplements. The agency tentatively concluded that there was not significant agreement among qualified experts that intakes of folic acid at levels permitted under the food additive regulation would be protective against occurrence of neural tube defects in pregnancies of women in the U.S. population.

In September 1992, while FDA's rulemaking was in progress, the U.S. Public Health Service (PHS)

¹ The term "folates" is a generic descriptor for a group of compounds that have nutritional properties and chemical structures similar to those of pterylglutamic acid, the parent form of the vitamins. Synthetic folic acid, added as a fortificant to foods, including dietary supplements, is the oxidized, monoglutamate form of the vitamin.

recommended, based on reviews of existing and newly available scientific data, that all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 milligram (mg) (400 micrograms (μ g)) of folic acid daily to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects (Ref. 1). The PHS recommendation noted that although all the effects of high intakes of folate are not well known, the effects do include complicating the diagnosis of vitamin B₁₂ deficiency. Therefore, the PHS recommended that care should be taken to keep total folate consumption at less than 1 mg per day except under the supervision of a physician.

On January 6, 1993 (58 FR 2606), the agency published a final rule in which it concluded that a health claim for folic acid and prevention of neural tube defects should not be authorized. The agency reaffirmed its support of the PHS recommendation that all women of childbearing age in the United States who are capable of becoming pregnant consume 0.4 mg of folic acid daily to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects. The agency noted, however, that questions about the safe use of folic acid in food remained, and the agency concluded that it could not authorize a health claim for folic acid until these questions, among others, were satisfactorily resolved.

Given the seriousness of neural tube defects and the safety and other concerns expressed in the PHS recommendation, FDA convened a subcommittee of its Food Advisory Committee to consider the issues concerning folic acid (hereinafter referred to as the "Folic Acid Subcommittee"). The Folic Acid Subcommittee met in November 1992 and in April 1993. FDA requested that the Folic Acid Subcommittee provide the agency with recommendations on several issues, including identification of the appropriate target population for a folate-neural tube defects health claim, the appropriate daily intake of folate to reduce the risk of neural tube defects, and safety concerns for the target population and the general population. One of the recommendations from the November 1992 meeting of the Folic Acid Subcommittee was that FDA attempt to design a fortification scheme that could provide 90 percent of women of childbearing age with at least 0.4 mg of folate per day from all sources, but would not result in excessively high folate intakes by nontarget groups.

At its April 1993 meeting, following expression of diverse opinions of the potential effectiveness of health claims

as an educational tool and by close votes by the Subcommittee members, the Folic Acid Subcommittee voted to support FDA actions to propose to authorize a health claim for folate and to propose to fortify cereal-grain products with folic acid. Based on the agency's discussion of the uncertainties in the intake data base and the difficulties in predicting bioavailability factors under differing conditions, the Folic Acid Subcommittee supported 1 mg as the safe daily upper limit for total folate from all sources.

The agency has now tentatively concluded, based on the totality of the scientific evidence, that there is significant scientific agreement supporting a relationship between folate and neural tube defects. The agency has also tentatively concluded that fortification of cereal-grains and breakfast cereals with folic acid is an appropriate means to increase the folate intake of women of childbearing age. Therefore, in documents published elsewhere in this issue of the *Federal Register*, FDA is proposing to: (1) Authorize the use on the label or in labeling of foods in conventional food form or of dietary supplements a claim concerning the relationship between folate and reduction in risk of neural tube birth defects (hereinafter referred to as the Health Claim proposal); and (2) require the addition of folic acid to enriched cereal-grain products (hereinafter referred to as the Standards of Identity proposal). The bases for these proposed actions and the safety issues considered by the agency are fully discussed in the Health Claim proposal.

FDA believes that if a health claim for the folate-neural tube defect relationship were authorized, food manufacturers would have an incentive to add folic acid to a wide variety of foods, which could lead to an increase in the intake of folate both by women in their childbearing years and by other segments of the general population. For example, in the *Federal Register* of January 6, 1993 (58 FR 2606), FDA presented an analysis showing that widespread fortification of the food supply with folic acid could lead to individual intakes in the range of 3 to 5 mg or more of folate per day. Because such an increase could bring with it certain risks, the agency is proposing to amend the food additive regulation for folic acid so that authorization of a health claim does not result in unsafe levels of folic acid in the diet.

B. Current Food Additive Regulation

In the *Federal Register* of August 2, 1973 (38 FR 20725), FDA published a final rule establishing safe conditions of

use for folic acid (folacin) in food and dietary supplements under § 121.1134 (21 CFR 121.1134). In determining the safe conditions of use for folic acid, the agency considered the Recommended Dietary Allowance established by the National Academy of Sciences, and other relevant information.

In 1977, § 121.1134 was recodified as § 172.345. The current food additive regulation states:

Folic acid (folacin) may be safely added to a food for its vitamin property, 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 milligram for foods labeled without reference to age or physiological state; and when age or the conditions of pregnancy or lactation are specified, in excess of 0.1 milligram for infants, 0.3 milligram for children under 4 years of age, 0.4 milligram for adults and children 4 or more years of age, and 0.8 milligram for pregnant or lactating women. (21 CFR 172.345)

The current regulation provides no guidance to manufacturers on how to comply with the stated limits. Information available to the agency, however, establishes that daily intakes of more than 1 mg of folate may place certain subpopulations at increased risk of masking the anemia associated with vitamin B₁₂ deficiencies. Other individuals that may be at risk due to increased intakes of folate include those receiving certain anticonvulsant or antifolate chemotherapies. The potential risks associated with chronic high exposure to folate are discussed in greater detail in the Health Claim proposal published elsewhere in this issue of the *Federal Register*. Thus, the current regulation is inadequate to allocate folic acid safely in the food supply.

Under section 409(c)(3)(A) of the act (21 U.S.C. 348(c)(3)(A)), the so-called "general safety clause" of the statute, a food additive cannot be approved for a particular use unless a fair evaluation of the evidence available to FDA establishes that the additive is safe for that use. FDA regulations grounded in the legislative history of the Food Additives Amendment of 1958 define "safe" as " * * * a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use." (21 CFR 170.3(i)).

Section 409(c)(5)(A) and (c)(5)(B) of the act require the agency to consider, in determining whether a proposed use of an additive is safe, the probable consumption of the additive and the cumulative effect of the additive in the diet of man. In the Health Claim

proposal published elsewhere in this issue of the *Federal Register*, the agency tentatively concludes, based upon the evidence currently available, that 1 mg per day is the safe upper limit of folate intake for all population groups. In light of this tentative conclusion, the agency has considered how it should amend its food additive regulations to establish safe conditions of use of folic acid in the food supply and still achieve the goals recommended by the Folic Acid Subcommittee that the target population, women of childbearing age, should consume at least 0.4 mg per day of folate from all sources while preventing excessively high intakes by nontarget groups.

Given the two goals of ensuring that the target population receives enough folate and ensuring that the general population is not placed at risk, FDA is proposing to amend the food additive regulation for folic acid (folacin) (§ 172.345) to confine the foods to which folic acid may be added to breakfast cereals and foods for which the standards of identity specifically require the addition of folic acid. This proposed rule also explicitly provides for the use of folic acid in infant formulas and in foods used under medical supervision, and does not change the current limitations on the use of folic acid in dietary supplements. Finally, this proposed rule establishes specifications for folic acid for use in food.

C. Safety Issues

The potential risks that may occur if the food supply were heavily fortified with folic acid were discussed in detail by FDA in the *Federal Register* of January 6, 1993 (58 FR 2806), and in the Health Claim proposal published elsewhere in this issue of the *Federal Register*; they are also summarized briefly here.

The ability of folates to mask the anemia of vitamin B₁₂ deficiency is the most widely recognized adverse effect of high intakes of the vitamin. In the presence of excess folic acid and inadequate vitamin B₁₂, the anemia of vitamin B₁₂ deficiency may not develop. However, severe and irreversible neurologic damage may occur and continue to progress (Ref. 2). Because of this risk, FDA has required warning statements in the labeling for oral and parenteral preparations of folic acid for therapeutic use, which statements describe the potential for the masking of pernicious anemia, a manifestation of vitamin B₁₂ deficiency (45 FR 69043, October 17, 1980; 36 FR 6843, April 9, 1971).

The potential for masking the anemia of vitamin B₁₂ deficiency was recognized by the September 14, 1992, recommendation of PHS, which stated: "Because the effects of high intakes are not well known but include complicating the diagnosis of vitamin B₁₂ deficiency, care should be taken to keep total folate consumption at <1 mg per day, except under the supervision of a physician" (Ref. 1).

As discussed in the Health Claim proposal published elsewhere in this issue of the *Federal Register*, vitamin B₁₂ deficiency is not an uncommon condition in the United States, nor is its diagnosis always straightforward. In general, the population most at risk of developing pernicious anemia is the elderly (Ref. 3). However, the average age of onset is variable among different ethnic groups in the United States (Refs. 4, 5, and 6). Other populations for whom high intakes of folate may pose risks include persons with epilepsy or who are taking certain anticonvulsant medications, persons taking drugs that interfere with folate metabolism, and pregnant women. The Health Claim proposal, published elsewhere in this issue of the *Federal Register*, includes a detailed discussion of the risks presented by excessive folate intake.

The agency's overriding responsibility in this food additive rulemaking is to ensure that the amount of folate that people are reasonably expected to consume is safe. The agency has examined the currently available data on the levels of folate that are capable of masking the anemia of vitamin B₁₂ deficiency, and tentatively concludes that the safe upper limit of daily intake of folate for the general population is 1 mg. The agency also tentatively concludes that 1 mg per day is a safe upper limit for other populations at risk. These tentative conclusions are based on: (1) The scientific evidence that the "masking" effect on vitamin B₁₂ deficiency is most likely to occur at levels of folate above 1 mg (see the Health Claim proposal published elsewhere in this issue of the *Federal Register* and Refs. 7 and 8); and (2) the support by the Folic Acid Subcommittee for FDA's use of 1 mg total folate per day as a safe upper limit to guide development of fortification options (Ref. 7); and (3) the PHS recommendation that " * * * care should be taken to keep folate consumption at <1 mg per day, except under supervision of a physician." (Ref. 1). This tentative conclusion concerning the safe daily upper limit for folate intake represents the agency's best scientific judgment at this time. The agency recognizes the significance of

this proposed upper limit to its analysis of the options for fortification of the food supply. FDA further acknowledges that this value may need to be adjusted based upon comments received on the three folic acid proposals.

D. Allocation of Folic Acid in Food Supply

1. Fortification Alternatives

In evaluating various options for increasing the folate intake of women of childbearing age, while at the same time not increasing the risk to the general population, FDA assessed the effect of various fortification and supplementation options on the estimated daily intake of folate. In developing these different options, the agency considered current use of folic acid as a food additive; a possible fortification of food categories that are widely consumed by the general population, e.g., dairy products, fruit juices, and cereal-grains; and dietary supplement use. The Health Claim proposal published elsewhere in this issue of the *Federal Register* discusses in detail the fortification options considered by the agency.

The agency determined, based upon available information, that the only conventional food category that currently enjoys widespread fortification with folic acid is breakfast cereal. The majority of breakfast cereals are fortified at 100 µg per serving (25 percent of the reference daily intake (RDI)). Other breakfast cereals contain 35 to 45 percent of the RDI for folate. There are a few breakfast cereals that contain 100 percent of the RDI for folate. The agency specifically requests comments as to whether there is currently widespread folic acid fortification of other food categories.

The agency also examined current practices with respect to consumption patterns of dietary supplements containing folic acid and the amount of folic acid that is routinely contained in dietary supplements. Many nationwide surveys conducted since 1970 show that 35 to 60 percent of the U.S. population consumes vitamin and mineral supplements. Park et al., (Ref. 9) reported the median potency of folic acid in single nutrient supplements was 125 percent of the RDI (range, 57 to 250 percent). In multinutrient supplements for children, folic acid was added at a level that provides approximately 75 percent of the RDI (range, 2 to 100 percent). The corresponding median potency values for prenatal supplements was 111 percent of the RDI (range, 50 to 125 percent), and for other supplements, 100 percent of the RDI (range, 1 to 500

percent) (Ref. 9). Thus, many supplements currently contain folic acid at or near 100 percent of the RDI (i.e., 0.4 mg or 400 µg for adults). This is consistent with the report by Werler et al. (Ref. 10), who determined that the most common dose of folic acid found in a variety of supplements was 0.4 mg (400 µg or 100 percent of the RDI).

FDA has considered a number of approaches to fortifying the food supply with folic acid. In particular, as described in the Health Claim proposal published elsewhere in this issue of the Federal Register, the agency examined the effect of fortification of the following food categories: Cereal grains, dairy products and fruit juices at 70, 140, and 350 µg folic acid per 100 g of food product. The agency also considered the effect on intake of adding 100 µg or 400 µg folic acid per serving to all breakfast cereals. In addition, in conducting this evaluation, the agency assumed that all dietary supplements contain 400 µg of folic acid. (The agency anticipates that if a health claim is allowed, the majority of dietary supplements will likely contain 100 percent of the RDI for folate (i.e., 400 µg)).

2. Proposed Folic Acid Fortification Approach

Upon examining the estimated folate intakes resulting from the different fortification options and in light of the agency's tentative conclusion that 1 mg per day is the safe upper limit of folate intake for the general population, the agency determined that the fortification scenario that best achieves the two goals of safety and effective delivery to the target population was one that limited the food additive use of folic acid to: (1) Enriched cereal-grains for which there exist standards of identity which authorize the addition of folic acid at 140 µg per 100 g; (2) breakfast cereals at levels up to 100 µg per serving; and (3) dietary supplements at levels up to 400 µg per daily dose, except for those labeled with reference to age or the condition of pregnancy or lactation.

Folic acid fortification of enriched cereal-grains offers the following advantages for delivery of folic acid to the target population: (1) Added folic acid is stable in the products derived from enriched cereal-grains; and (2) consumption of products manufactured with enriched cereal-grains is widespread throughout the population, including the target population. Therefore, the agency has tentatively concluded that folic acid fortification of enriched cereal-grain products is an effective way to increase the folic acid intake of women of childbearing age. Consistent with this tentative

conclusion, in a document published elsewhere in this issue of the Federal Register, the agency is proposing to amend the regulations for the standards of identity of the following enriched cereal-grain products: enriched bread, rolls, and buns (§ 136.115); enriched flour (§ 137.165); enriched self-rising flour (§ 137.185); enriched corn grits (§ 137.235); enriched corn meals (§ 137.260); enriched farina (§ 137.305); enriched rice (§ 137.350); enriched macaroni products (§ 139.115); enriched nonfat milk macaroni products (§ 139.122); and enriched noodle products (§ 139.155).

FDA has tentatively determined that the addition of folic acid to breakfast cereals at levels up to 100 µg per serving is an appropriate means to provide added folic acid because: (1) Breakfast cereal is the only food category that currently enjoys widespread fortification with folic acid and such cereals represent a traditional source of many nutrients, including folic acid, for those who consume them; and (2) due to patterns of consumption, fortification of breakfast cereals at 100 µg folic acid per serving should not result in excessive folate intakes in the nontarget population. FDA considered, and has tentatively rejected, a proposed regulation that would have allowed for addition of up to 400 µg folic acid per serving in breakfast cereal, because this level would have resulted in the estimated daily intake of folic acid among significant portions of the population exceeding what has been tentatively identified as the safe upper limit of 1 mg per day. These excess levels would have occurred even in the absence of the fortification of enriched cereal-grains.

The agency has tentatively concluded that it should continue to allow the addition of folic acid up to 400 µg per daily dose in dietary supplements because: (1) There is a documented history of safe use of dietary supplements at this level (Ref. 9), and (2) dietary supplements containing higher levels of folic acid are not appropriate except in specific circumstances (i.e., conditions of pregnancy or lactation) because of the identified safety concerns, particularly the masking of vitamin B₁₂ deficiencies.

As noted above, in developing this proposal, the agency examined several fortification scenarios. In tentatively choosing a fortification approach, the agency's concern was the safety of the food supply. FDA recognizes that it is impossible for the agency to examine all possible fortification scenarios. The agency requests comments on possible alternative fortification approaches that

will achieve FDA's dual goals of maximizing delivery of folate to the target population and ensuring the safety of such uses of folic acid. Thus, comments on alternative fortification schemes should address issues related to the safety of the exposures that would result from the proposed alternative scheme.

E. Proposed § 172.345

In this rulemaking, the agency is proposing to: (1) Establish a limitation for the addition of folic acid to breakfast cereals, of 0.1 mg folic acid per serving; (2) retain current limitations for the use of folic acid in dietary supplements; (3) permit the addition of folic acid to foods as authorized by standards of identity established under section 401 of the act (21 U.S.C. 341); (4) explicitly allow for the use of added folic acid in infant formulas and in foods to be used under medical supervision; and (5) establish specifications for folic acid that are consistent with those in the Food Chemicals Codex (3d ed.) (Ref. 9).

1. The agency is proposing in § 172.345(d) to limit the added folic acid in breakfast cereals, as defined under 21 CFR 170.3(n)(4), to 100 µg per serving.

FDA recognizes that this proposed action will have the effect of requiring the reformulation of a small number of breakfast cereals. It is not the agency's desire to have such an effect, but it appears to be unavoidable given the data and information currently available to the agency. The agency is prepared to reconsider this approach for breakfast cereals if interested persons submit comments that provide data or other information demonstrating that even with higher fortification of breakfast cereals, folate consumption can be kept within safe limits.

The agency is particularly interested in obtaining substantive comments on the fortification option tentatively chosen by the agency. In addition, FDA expressly seeks: (1) Comments on the use of 1 mg per day total folate as a safe upper limit for establishing restrictions on food additive uses of folic acid; (2) comments that address issues related to folic acid intake and adverse effects; and (3) comments that provide information pertaining to the proposed limitations of 100 µg per serving of folic acid in breakfast cereals.

FDA recognizes that some may find an inequity in the agency's treatment of dietary supplements, with respect to which the agency is proposing to allow continued marketing of a 400 µg folic acid supplement, as compared to the agency's treatment of breakfast cereals, with respect to which FDA is proposing to establish a 100 µg per serving limit

for folic acid. FDA has tentatively determined that this approach is appropriate because supplements tend to be used to supplement the diet for specific purposes, while breakfast cereals are used more generally as part of the overall diet. However, the agency specifically requests comments on this issue. Although comments may suggest alternate approaches, such comments will be most useful if they explain how the suggested approach will ensure that total dietary intake of folate will remain within what are shown to be safe levels.

The agency finds that current limitations based on daily intake levels for added folic acid are impractical and require clarification, especially if a health claim is authorized. In light of the recent establishment of new food labeling format requirements (58 FR 2079, January 6, 1993), FDA also finds that establishing limitations based on a "per serving" basis would be more consistent with the new food labeling format and more informative because it would provide the consumer with a consistent basis upon which the nutritive value of food products can be compared. Therefore, the agency is proposing to amend the language of its regulation to establish use limitations on a "per serving" basis.

2. In § 172.345(f), the agency is proposing to maintain current limitations on the use of folic acid in dietary supplements. As discussed in the Health Claim proposal published elsewhere in this issue of the **Federal Register**, the agency has concluded that the current limitation of 400 µg per daily dose in supplements labeled without reference to age or physiological status is safe and the agency does not anticipate that unsafe intakes of folate will occur if the current limitation is maintained.

3. In § 172.345(c), the agency is proposing to amend the current food additive regulation to allow for addition of folic acid in accordance with standards of identity established under section 401 of the act. In the Standards of Identity proposal published elsewhere in this issue of the **Federal Register**, the agency is proposing to amend the standards of identity for a number of cereal-grain products to require folic acid fortification at a level of 140 µg per 100 g.

4. In § 172.345(e), the agency is proposing to amend the current food additive regulation by explicitly permitting addition of folic acid to infant formulas, consistent with section 412 of the act and regulations promulgated thereunder.

5. In § 172.345(g), the agency is proposing to amend the current food

additive regulation by exempting foods used under medical supervision from limitations, other than good manufacturing practices, on the amount of folic acid that may be added.

6. In § 172.345(b), the agency is proposing to amend the current food additive regulation by incorporating by reference specifications for folic acid added to food to make the regulation consistent with the Food Chemicals Codex specifications (Ref. 11).

The agency tentatively concludes that this proposed rule provides a reasonable certainty of no harm because, as discussed above and in the Health Claim proposal, the estimated daily intakes of folate in the population do not exceed 1 mg per day, which is the level that has been tentatively identified as the safe upper limit of exposure.

II. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Because the agency is proposing three actions involving folic acid and the net effect of these actions is likely to increase the use of folic acid, one environmental assessment has been prepared, which considers all three proposed actions.

III. Economic Impact

FDA has examined the economic implications of the proposed rule as required by the Regulatory Flexibility Act and Executive Order 12291. The Regulatory Flexibility Act (Pub. L. 96-354) requires regulatory relief for small businesses where feasible. Executive Order 12291 compels agencies to use cost-benefit analysis as a component of decisionmaking, where permitted by law. The agency finds that this proposed rule is not a major rule as defined by Executive Order 12291. In compliance with the Regulatory Flexibility Act, FDA certifies that the proposed rule will not have a significant impact on a substantial number of small businesses.

The agency is proposing to restrict the use of folic acid as a food additive only to breakfast cereals, dietary supplements, foods for special dietary use, infant formula, and any standardized foods which are required to contain folic acid. If the proposed

rule is finalized, some products that currently contain folic acid as an ingredient will have to be reformulated because they do not fall into the categories listed above. The agency does not have information on how many products will have to be reformulated. However, as far as FDA is aware, the only intended technical effect of adding folic acid to food is to supplement the nutritional content of the food. Thus, the reformulation should not be costly nor should it have any measurable adverse impact on the consumer demand for the products. FDA estimates the cost of the proposed rule to be minimal.

FDA is proposing to take this action in order to prevent health risks associated with high intakes of folate in the event that the standards of identity for enriched grain products are amended to require the addition of folic acid and that a health claim is permitted for folates and neural tube defects. FDA is not able to quantify the benefit of the proposed rule because it is not able to estimate the extent to which folate health claims will be made or the effect that claims will have on consumer demand for products containing added folic acid.

IV. Comments

During the comment period for this proposal, the agency intends to convene public meetings of the Folic Acid Subcommittee and the Food Advisory Committee for a discussion of the issues raised in this document, as well as the Health Claim proposal and the Standards of Identity document. FDA also intends to request comments from the experts who participated in its November 23 and 24, 1992, meeting of the Folic Acid Subcommittee. The agency will make any comments received from these experts available for public review and comment. In addition, FDA will endeavor to have copies of the transcripts of the Folic Acid Subcommittee and Food Advisory Committee meetings available as quickly as possible.

Interested persons may, on or before December 13, 1993, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

V. 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.

1. Centers for Disease Control, "Recommendations for the Use of Folic Acid to Reduce the Number of Cases of Spina Bifida and Other Neural Tube Defects," *Morbidity and Mortality Weekly Reports*, 41:1-7, 1992.

2. Butterworth, C. E., and T. Tamura, "Folic Acid Safety and Toxicity: A Brief Review," *American Journal of Clinical Nutrition*, 50:353-358, 1989.

3. Herbert, V., N. Coleman, and E. Jacob, "Folic Acid and Vitamin B₁₂," in *Modern Nutrition in Health and Disease*, 6th ed., edited by Goodhart, R. S. and M. Shils, Lea and Febiger, Philadelphia: pp. 249-250, 1980.

4. Carmel, R., and S. C. Johnson, "Racial Patterns in Pernicious Anemia: Early Age at Onset and Increased Frequency of Intrinsic Factor Antibody in Black Women," *New England Journal of Medicine*, 296:647-650, 1978.

5. Solanki, D. L., R. J. Jacobson, and R. J. Green, et al., "Pernicious Anemia in Blacks: A Study of 64 Patients From Washington, DC and Johannesburg, South Africa," *American Journal of Clinical Pathology*, 75:96-99, 1981.

6. Sinow, R. M., C. S. Johnson, and D. S. Karnaze, et al., "Unsuspected Pernicious Anemia in a Patient With Sickle Cell Disease Receiving Routine Folate Supplementation," *Archives of Internal Medicine*, 147:1828-1829, 1987.

7. Transcript of meeting of the Food Advisory Committee, Subcommittee on Folic Acid, November 23-24, 1992.

8. Transcript of meeting of the Food Advisory Committee, Subcommittee on Folic Acid, April 15, 1993.

9. Park, Y. M., I. Kim, and E. A. Yetley, "Characteristics of Vitamin and Mineral Supplement Products in the United States," *American Journal of Clinical Nutrition*, 54:750-759, 1991.

10. Werler, M. M., S. Shapiro, and A. A. Mitchell, "Periconceptional Folic Acid

Exposure and Risk of Occurrent Neural Tube Defects," *Journal of the American Medical Association*, 269:1257-1261, 1993.

11. Food Chemicals Codex, 3d ed., pp. 125 and 126, Washington, DC: National Academy Press, 1981.

List of Subjects in 21 CFR Part 172

Food additives, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 172 be amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

1. The authority citation for 21 CFR part 172 continues to read as follows:

Authority: Secs. 201, 401, 402, 409, 701, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 342, 348, 371, 379e).

2. Section 172.345 is revised to read as follows:

§ 172.345 Folic acid (folacin).

Folic acid (CAS Reg. No. 59-30-3), also known as folacin or folate, may be safely used in food as a nutrient in accordance with the following prescribed conditions:

(a) Folic acid is the chemical N-[4-[[[(2-amino-1,4-dihydro-4-oxo-6-pteridiny)]methyl]amino]benzoyl]-L-glutamic acid.

(b) Folic acid meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), pp. 125 to 126, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies may be obtained from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(c) Folic acid may be added to foods as authorized by standards of identity established under section 401 of the act.

(d) Folic acid may be added, at levels not to exceed 100 micrograms (µg) per serving, to breakfast cereals, as defined under § 170.3(n)(4) of this chapter.

(e) Folic acid may be added to infant formula in accordance with section 412(i)(2) of the Federal Food, Drug, and Cosmetic Act (the act) or with regulations promulgated under section 412(b)(1) of the act.

(f) Folic acid may be added to a dietary supplement that is a food, other than in conventional food form, that supplies a component with nutritive value to supplement the diet by increasing the total dietary intake of folic acid, provided that the maximum intake as directed for use will not result in daily ingestion of the additive in excess of 400 µg for foods labeled without reference to age or physiological state; and when age or conditions of pregnancy or lactation are specified, daily ingestion of folic acid may not exceed 100 µg for infants, 300 µg for children under 4 years of age, 400 µg for adults and children 4 or more years of age, and 800 µg for pregnant or lactating women.

(g) Folic acid may be added to special dietary foods that are intended for use solely under medical supervision to meet nutritional requirements in specific medical conditions and that comply with the requirements of part 105 of this chapter. Folic acid may be used in such foods at levels not to exceed the amount reasonably required to accomplish its intended nutritive effect.

Dated: September 13, 1993.

David A. Kessler,

Commissioner of Food and Drugs.

[FR Doc. 93-25028 Filed 10-7-93; 2:51 pm]

BILLING CODE 4160-01-F