(v) *Prevalence.* The claim may provide estimates, expressed on an annual basis, of the number of neural tube defect-affected births among live births in the United States. Current estimates are provided in § 101.79(b)(1), and are approximately 6 of 10,000 live births annually (i.e., about 2,500 cases among 4 million live births annually). Data provided in § 101.79(b)(1) shall be used, unless more current estimates from the U.S. Public Health Service are available, in which case the latter may be cited.

(vi) *Reduction in risk.* An estimate of the reduction in the number of neural tube defect-affected births that might occur in the United States if all women consumed adequate folate throughout their childbearing years may be included in the claim. Information contained in paragraph (b)(3) of this section may be used. If such an estimate (i.e., 50 percent) is provided, the estimate shall be accompanied by additional information that states that the estimate is population-based and that it does not reflect risk reduction that may be experienced by individual women.

(vii) *Diets adequate in folate.* The claim may identify diets adequate in folate by using phrases such as ''Sources of folate include fruits, vegetables, whole grain products, fortified cereals, and dietary supplements.'' or ''Adequate amounts of folate can be obtained from diets rich in fruits, dark green leafy vegetables, legumes, whole grain products, fortified cereals, or dietary supplements.'' or ''Adequate amounts of folate can be obtained from diets rich in fruits, including citrus fruits and juices, vegetables, including dark green leafy vegetables, legumes, whole grain products, including breads, rice, and pasta, fortified cereals, or a dietary supplement.''

(d) *Model health claims.* The following are examples of model health claims that may be used in food labeling to describe the relationship between folate and neural tube defects:

(1) *Examples 1 and 2.* Model health claims appropriate for foods containing 100 percent or less of the DV for folate per serving or per unit (general population). The examples contain only the required elements:

(i) Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect.

(ii) Adequate folate in healthful diets may reduce a woman's risk of having a child with a brain or spinal cord birth defect.

(2) *Example 3.* Model health claim appropriate for foods containing 100 percent or less of the DV for folate per serving or per unit. The example contains all required elements plus optional information: Women who consume healthful diets with adequate folate throughout their childbearing years may reduce their risk of having a child with a birth defect of the brain or spinal cord. Sources of folate include fruits, vegetables, whole grain products, fortified cereals, and dietary supplements.

(3) *Example 4.* Model health claim appropriate for foods intended for use by the general population and containing more than 100 percent of the DV of folate per serving or per unit: Women who consume healthful diets with adequate folate may reduce their risk of having a child with birth defects of the brain or spinal cord. Folate intake should not exceed 250% of the DV (1,000 mcg).

Dated: February 26, 1996.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 136, 137, and 139

[Docket No. 91N–100S]

RIN 0910–AA19

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the standards of identity for several enriched grain products and, by cross-reference, the standards of identity for enriched bromated flour, enriched vegetable macaroni, and enriched vegetable noodle products, to require the addition of folic acid. The agency is requiring 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 (μg) to 309 μg/100 grams (g), of product. These values are based on a fortification level of 140 μg/100 g (0.635 mg/lb) of the cereal grain product. This action is being taken to help women of childbearing age to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects (NTD's) and to comply with the recommendation of the U.S. Public Health Service (PHS) that they consume at least 0.4 mg (400 μg) of folic acid daily. This action also responds to a citizen petition submitted by Glenn Scott.

EFFECTIVE DATE: January 1, 1998.

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

Recent estimates state that there are approximately 4,000 pregnancies each year, including 2,500 live births, that are affected by spina bifida and other neural tube defects. In September 1992, PHS recommended that all women of childbearing age in the United States consume 0.4 mg (400 μg) of folic acid daily to reduce their risk of having a pregnancy affected with spina bifida or other NTD's (Ref. 1). Furthermore, PHS identified several possible approaches by which folate intake by the target population could be increased. These approaches included: (1) Improvement of dietary habits, (2) fortification of the U.S. food supply, and (3) daily use of folic acid supplements by women throughout their childbearing years. However, the PHS recommendation cautioned against daily intakes of folate above 1 mg. A recognized adverse effect of high intakes of folate is a masking of the anemia of vitamin B12 deficiency, allowing the neurologic damage to progress untreated. PHS noted 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).

Following publication of the PHS recommendation, FDA convened a Folic Acid Subcommittee from its Food Advisory Committee (hereinafter referred to as the Folic Acid Subcommittee) to consider some of the issues raised by the recommendation. After consideration debate, the Folic Acid Subcommittee identified several approaches that might assist women of childbearing age to increase their daily folate intake. These approaches included: (1) Development of a fortification program such that 90 percent of women of childbearing age could receive at least 400 μg 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 pregnancy, and continuing into early pregnancy and its potential effect on reducing the incidence of NTD's. (For a detailed discussion of the issues and concerns raised by the Folic Acid Subcommittee please refer to the Health Claims proposed rule (58 FR 23254 at 23256) and the final rule authorizing a health claim about the relationship between folate and neural tube defects (hereinafter referred to as the claims final rule) published elsewhere in this issue of the Federal Register.)

After considering the suggestions of PHS and the Folic Acid Subcommittee, FDA tentatively concluded that development and implementation of a fortification program for the addition of folic acid to the food supply could be an effective part of an overall plan to increase the folate intake of women of childbearing age to assist them in reducing their risk of having a NTD-affected pregnancy. Food fortification, as noted by the Folic Acid Subcommittee and expert speakers who testified before the Folic Acid Subcommittee, has the advantage of reaching a great number of women in the target population before conception and during early pregnancy. It also has the advantage of providing folic acid in a continuous and passive manner and, thus, represents a potentially effective means for improving the folate nutriture of women throughout their childbearing years. However, fortification must be controlled to ensure that daily intake of folate by the target population, as well as by the general population, is no more than 1 mg.

The issues raised by a fortification program were highlighted for the agency in the Federal Register of October 14, 1993 (58 FR 53254), in a document entitled ''Food Labeling: Health Claims and Label Statements; Folate and Neural Tube Defects,'' (hereinafter referred to as the folic acid health claims proposal) when it proposed to authorize a health claim about the relationship between folate and the risk of neural tube birth defects on the labels or in the labeling of foods and dietary supplements. In the folic acid health claims proposal (58 FR 53254 at 53270), FDA acknowledged that authorizing a health claim on folate and NTD's would create the likelihood that manufacturers would fortify their products with folic acid so that they could qualify to bear the claim, thereby increasing the possibility of uncontrolled fortification of the food supply. Consequently, FDA said that any fortification program that it adopted must be consistent with a safe range of intake for all population groups and yet be capable of maximizing the folate intakes of the target population within this safe range.

The options that FDA considered for providing folic acid to women of childbearing age through food fortification included the addition of folic acid to cereal-grain products, fruit juices, and dairy products. In weighing these options, FDA considered the effects of the inclusion of folic acid in breakfast cereals and in dietary supplements. The agency's decision to factor the amount of folic acid supplied by breakfast cereals and supplements in its estimates of the effects of fortification is fully discussed in the folic acid health claims proposal (58 FR 53254 at 53276).

In determining the appropriate levels of fortification with folic acid, the agency used the U.S. Department of Agriculture's (USDA's) 1987 to 1988 national food consumption data (Ref. 2) to estimate the daily intake of folate for the target population, as well as for the general population, with fortification at different levels for cereal-grain products, dairy products, and juices. The agency estimated the effects of fortification using three values: 70, 140, and 350 µg of folic acid/100 g of cereal-grain product. As discussed in the folic acid health claims proposal, the value of 70 µg/100 g (0.317 µg/lb) is the amount recommended in 1974 by the Food and Nutrition Board, National Research Council, National Academy of Sciences, and would restore the folate lost in the milling of cereal-grain products (Ref. 3). The value of 140 µg/100 g is twice that amount, and 350 µg/100 g is five times that amount.

FDA's analysis showed that when fortification included fruit juices and dairy products in addition to cereal-grain products, ready-to-eat breakfast cereals, and dietary supplements, intakes by consumers in some nontarget groups exceeded 1 mg/day even at the lowest level of fortification. However, when fortification is limited to cereal-grain products at levels of 70 µg/100 g or 140 µg/100 g, estimates of daily intakes remained below 1 mg/100 g. At fortification levels of 350 µg/100 g, FDA estimated the daily intake to reach levels of 1,220 µg/day, 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 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 1 mg/day.

These estimates showed that consumers who followed even the low-end of recommendations from the 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/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 tentatively determined that fortification should be limited to cereal-grain products and not extended to dairy products and fruit juices. The agency noted that intakes by very large segments of the general population could reach several milligrams per day if all of these foods were fortified with folic acid.

The agency also tentatively decided that the appropriate fortification level for cereal-grain products was 140 µg/100 g. Based on the results of its analysis, FDA determined that fortification of cereal-grain products with 140 µg/100 g, along with fortification of ready-to-eat breakfast cereals up to 100 µg/serving and dietary supplements up to 400 µg per unit or per serving, would provide increased intakes of folate for women in their childbearing years, while keeping daily intakes for the nontarget population within the recommended safe upper limit of approximately 1 mg/day. The agency noted that even 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 recognized that this level approached the recommended safe upper limit and did not take into account likely underreporting biases regarding food intakes and underestimation of folate content of foods, it tentatively concluded that fortification of cereal-grain products with 140 µg/100 g folic acid was the most appropriate fortification level of the three levels analyzed.

In addition to estimating daily intakes of folate at the levels cited above, FDA reviewed the existing food additive regulation § 172.345 (21 CFR 172.345) governing the use of folic acid to determine whether the regulation was adequate to ensure that addition of folic acid to foods would be consistent with

the fortification proposals discussed above. As a result of its review, FDA recognized that the existing regulation lacked the guidance necessary for manufacturers to decide which foods are appropriate for fortification, and the levels at which folic acid can be added. More importantly, FDA realized that the regulation would not have limited the addition of folic acid to enriched cereal-grain products, breakfast cereals, and dietary supplements. In fact, the regulation as written would have permitted folic acid addition to virtually any food.

Thus, in the same issue of the Federal Register that the agency proposed to authorize a health claim about the relationship of folate and NTD's (58 FR 53254 at 53270), it published a proposal entitled ''Food Additives Permitted for Direct Addition to Food for Human Consumption, Folic Acid (Folacin)'' (58 FR 53312) (hereinafter referred to as the food additives proposal) to amend the food additive regulation to restrict the addition of folic acid to specific foods. In that document, FDA proposed, among other things, to establish a limitation on the addition of folic acid to breakfast cereals of 100 µg folic acid per serving, to retain current limitations (i.e., 400 µg/daily) on the use of folic acid in dietary supplements, and to permit the addition of folic acid to foods as authorized by the standards of identity. The agency tentatively concluded that such action was necessary to establish safe conditions of use for folic acid in the food supply and still assist the target population, women of childbearing age, to achieve the goal recommended by PHS that they consume at least 400 µg of folate per day.

Also, in the October 14, 1993, issue of the Federal Register, FDA published a proposal entitled ''Food Standards: Amendment of the Standards of Identity for Enriched Grain Products to Require Addition of Folic Acid,'' (58 FR 53305) (hereinafter referred to as the standards of identity proposal) to amend the following standards of identity to require the addition of folic acid at a fortification level of 140 µg/100 g: 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)) and, by cross-reference, 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)).

FDA received approximately 170 letters in response to its proposal to amend the standards of identity for enriched cereal-grain products to require folic acid fortification at 140 µg/100 g. Each letter contained one or more comments. The letters were from a wide range of sources, including individual members of FDA's Folic Acid Subcommittee and Food Advisory Committee, Federal and State Government agencies, a foreign government, health care organizations, academia, consumer organizations, medical professionals, consumers, industry, and industry trade associations. Some comments supported various provisions of the proposal. Other comments suggested modifications, revisions, or revocations of various provisions of the proposal. Some comments raised concerns that were more germane to issues discussed in the folic acid health claims and food additive proposals. These comments were forwarded to the appropriate dockets for response. Some comments raised issues that were outside the scope of this rulemaking and will not be addressed in this final rule. A summary of the relevant comments, the agency's responses to the comments, and a complete discussion of the agency's conclusions with respect to the fortification of enriched cereal-grain products follow.

II. Comments and Agency Response

A. Fortification

1. The majority of comments recognized the need to assist women of childbearing age to increase their daily intake of folate to reduce their risk of an NTD-affected pregnancy. Many of these comments agreed with the PHS' and Folic Acid Subcommittee's recommendations that fortification of the food supply is an appropriate approach to achieve this goal. Several comments, however, opposed the use of fortification as a mechanism to address this need. Some of the comments opposed fortification because of uncertainties in the efficacy data. These comments stated that the available data do not indicate what minimum level of folate is needed to effect a significant reduction in NTD's, and they argued that, therefore, the decision to fortify is premature. These comments suggested that the agency wait until additional studies have been completed that better define the minimum level of folate needed to be effective or that identify other alternatives that would be effective in increasing the daily folate intake of the target population.

While FDA recognizes that there is some uncertainty in the literature as to the optimal intake of folate required to reduce the risk of NTD's, PHS, in examining the data from the available human studies, found the evidence sufficiently consistent to make its recommendation that all women capable of becoming pregnant should consume 400 µg folic acid daily. This target intake goal represents the best scientific judgment based on available data. It has also been supported by the Folic Acid Subcommittee.

Furthermore, PHS, the Folic Acid Subcommittee, as well as other medical experts, recommended food fortification as part of an overall program to improve the folate intake of women of childbearing age. This recommendation is based on the fact that 50 percent of pregnancies are unplanned, and that a large segment of women in the target group will not use folic acid supplements daily. Thus, a passive means of ensuring that these women have adequate folate intake is important. The comments that opposed fortification did not submit any data in support of their position. Thus, the agency has no basis to reject the recommendations of PHS and the Folic Acid Subcommittee to develop a folate fortification program to assist women of childbearing age in consuming at least 400 µg/day.

Although the agency is aware that there are several ongoing studies on the relationship between folate and NTD's, it has not been persuaded by the comments to wait until additional studies have been completed to determine what minimum level of folate intake is likely to be effective. The agency has confidence in the data that suggest that at intake levels of 400 µg/day, the incidence of NTD's can be reduced. Thus, the agency concludes that it would not be in the best interest of women in the target group to wait until these studies are completed and reviewed before implementing a program to assist them in increasing their daily intake of folate.

The evidence that is available supports the position that the consumption of folate plays an important role in reducing the risk of neural tube birth defects. Weighing this evidence and recognizing that the majority of women in the target population do not consume the levels of

folic acid recommended to reduce the risk of neural tube birth defects (Ref. 1), the agency concludes that it is appropriate to implement a fortification program at this time.

Further, the agency is concerned that without the limitations that it is adopting in this final rule, and in the final rule entitled ''Food Additives Permitted for Direct Addition to Food for Human Consumption; Folic Acid (Folacin)'' (hereinafter referred to as the food additives final rule) which is published elsewhere in this issue of the Federal Register, to control the addition of folic acid to the food supply, the authorization of the health claim about folate and NTD's may encourage overfortification of the U.S. food supply and increase the risk of overconsumption of folate. Because the current food additive regulation does not limit or specify the types of foods that can be fortified with folic acid, approval of the claim, without any other action by the agency, could encourage manufacturers to fortify a variety of foods to qualify the food for a health claim. Consequently, without proper control over the types of foods that can be fortified with folic acid, overfortification could result.

The amendment to the standards of identity for enriched cereal-grain products to require the addition of folic acid at specific levels will help to ensure that the addition of folic acid to the food supply is done in a safe, rational, and reasonable manner because it will limit the number of foods that can be fortified and limit the level of fortification. The levels of fortification established in this final rule, coupled with the provisions governing addition of folic acid to nonstandardized foods established in the food additives final rule, will meet the goal of increasing folate intake among women of childbearing age while keeping the daily consumption of folate below the safe upper limit of 1 mg/day.

2. Comments that opposed fortification asserted that consumers believe that fortification as proposed denies freedom of choice and control over daily folate intake and is, therefore, viewed as an attempt to medicate people without obtaining informed consent. These comments further asserted that fortification, as proposed, subjects them to the risk of overconsumption. As an alternative, these comments suggested that the effort to increase dietary folate intake in the target population focus on the use of dietary supplements because the amount of intake can be better controlled. They suggested that FDA work with other public health service agencies to establish policy initiatives equivalent to those used by the food and dietary supplement industries to market their products.

The agency disagrees with these comments. The agency is providing for fortification with folic acid only in the standards of identity for enriched cereal-grain products. Unenriched cereal-grain products without folic acid will continue to be available. Consumers will be able to select foods made with the unenriched version of the product if they wish to avoid folic acid. Furthermore, the estimated daily intakes that will result from the level of fortification established in this final rule are well below the level of folic acid traditionally used to treat persons with folate deficiency. Therapeutic dosages of folic acid used for treatment of folate deficiency are generally in the range of 1 to 5 mg/day and are administered under the supervision of a physician. Therefore, the comments that suggest that fortification of enriched cereal-grain products is an attempt to medicate the U.S. population simply have no basis in fact.

Furthermore, the intakes that are likely to result from the level of fortification established in this final rule do not present a health concern to the general population, especially in conjunction with the provisions of the food additive final rule published elsewhere in this issue of the Federal Register. FDA has projected the total daily intake of folate that is likely to result from the levels of fortification that FDA is requiring and determined that it is well within the safe upper limit of intake. Moreover, cereal-grain products have a long history of being vehicles for improving the nutrient intake of the U.S. population. FDA requires the addition of niacin, thiamin, and riboflavin in the standards of identity for enriched cereal-grain products to improve the daily intake of these nutrients. Fortification of these products was instrumental in reducing the prevalence of diseases related to insufficient intake of these vitamins.

In response to the comments that suggested that FDA rely on the use of dietary supplements to increase daily folate intake, the agency notes that in requiring the fortification of enriched cereal-grain products, it is not discounting the use of dietary supplements to assist women in the target group to increase their daily folate intake. In fact, the agency included the use of dietary supplements in its estimates to determine the appropriate level for fortification of enriched cereal-grain products. However, the agency is not confident that the use of dietary supplements alone will be sufficient to reach the target population when folate intake is critical (i.e., before and during the first 6 weeks of pregnancy).

During the first 6 weeks of pregnancy many women are not even aware that they are pregnant and would likely not be under the care of a physician. Thus, as stated in several comments, there would be no reason to expect the many women who do not normally take supplements daily to be motivated to change this behavior. Therefore, supplement use cannot be relied on as the sole source for increasing dietary folate intake. As discussed above, the use of fortification of cereal-grain products has the advantage of providing folic acid in a continuous and passive manner and, therefore, should be an effective means for improving the folate nutriture of women in their childbearing years.

3. A few comments opposed to fortification suggested that, as an alternative, FDA encourage women in the target group to increase their daily folate intake by increasing consumption of foods that naturally contain high levels of folate such as blackeye peas.

While FDA finds merit in the comments' suggestion to encourage women in the target group to increase their daily folate intake by increasing their consumption of foods naturally high in folate, the agency is not persuaded that such action makes food fortification unnecessary. The dietary guidance suggested by the comment can be used in conjunction with food fortification, as part of a program designed to help women in the target group to increase their daily folate consumption. A health claim about the relationship between folate and NTD's on a food that qualifies to bear the claim will contribute to such a program, regardless of whether the food naturally qualifies to bear the claim or qualifies on the basis of its fortification level. In addition, foods that naturally contain folate and qualify to bear a health or nutrient content claim are likely to be highlighted as a source of this nutrient. Such claims will encourage women in the target group to select these foods as a part of their diet.

Most significantly, however, given the value of adequate folate intake by women of childbearing age and given the value of a program that allows women to obtain adequate folate by simply consuming such staples as bread and rolls, FDA sees no reason not to require fortification of such foods, even though foods exist that are naturally high in folate.

4. Some comments opposed to fortification opined that fortification

would not assure physicians and health care professionals that their patients are obtaining adequate amounts of folate from the food supply because the bioavailability of folate in foods is 25 to 75 percent depending on the food.

As discussed in the folic acid health claims proposal, FDA considered several issues in developing its options for fortification. With respect to issues of bioavailability, FDA concluded that bioavailability cannot be meaningfully factored into fortification scenarios because issues of bioavailability are very complex, and no systematic data are available on many of the factors that affect bioavailability. Consequently, the estimates developed by FDA focused more on consumption patterns of various staple foods, and their availability and use in the U.S. food supply, than on the bioavailability of folic acid from a specific food.

The comment did not provide information to persuade the agency that the complexity associated with bioavailability would significantly reduce the effectiveness of food fortification as part of an overall effort to improve folate nutriture among women in the target group.

5. Two comments recommended revising the proposal to require the addition of vitamin B_{12} in a one-to-one ratio with folic acid. The comments contended that doing so will not only prevent vitamin B_{12} deficiency, but it will also prevent the masking effect that may be caused with high consumption of folate. One comment urged FDA to design research that will determine the safety and effectiveness of fortifying the food supply with vitamin B_{12} along with folic acid because such fortification could eliminate the adverse effect of folate on vitamin B_{12} deficiency.

The agency is not persuaded that the approach suggested by these comments addresses all of the safety concerns relating to persons with vitamin B_{12} deficiencies. As fully discussed in the food additives final rule, FDA rejects this recommendation because the available data do not establish that requiring the addition of vitamin B_{12} whenever folic acid is added will eliminate the safety concerns relating to persons with vitamin B_{12} deficiencies that arise because of deficiencies in intrinsic factor (pernicious anemia) or other B_{12}-related deficiencies.

6. Two comments opposed to fortification stated that FDA should take the same position with respect to folic acid fortification that it did when it decided not to fortify foods with iron in the 1970's because of the concern about iron storage diseases.

While the agency acknowledges that it considered taking a similar approach to increase the amount of iron provided by the diet when it proposed to double the amount of iron added to enriched cereal-grain products, the agency did not finalize that proposal because of significant safety concerns regarding the risk of iron storage diseases. Rather, the agency retained the existing level of iron fortification for cereal-grain products. The agency does not have similar safety concerns about the level of folic acid fortification that it is requiring in this final rule because it has concluded, based on a safety review (as fully discussed in the food additives proposal and final rule), that this required level is safe and will not result in overconsumption of folate.

B. Covered Products

7. Some comments stated that dietary consumption studies indicate that women of reproductive age are less likely than other groups to consume enriched cereal-grain products that conform to a standard of identity, and that, therefore, the use of such foods as a vehicle for folic acid fortification would not significantly affect the risk of NTD's. These comments argued that, instead, fortifying these foods will only increase the amount of daily folate intake among the nontarget groups.

In selecting cereal-grain products as vehicles for fortification, the agency started with the basic principle that fortification of staple products that are commonly consumed in significant amounts by virtually all members of the target population is most likely to result in increased intakes of a specific nutrient by the target population. Although the agency recognizes that current survey data suggest that consumption of enriched grain products may be somewhat lower in the target population than in other groups, these foods still are reported to be consumed on a daily basis by more than 90 percent of women of childbearing age (Ref. 4). In addition, data show that the difference between target and nontarget populations in consumption of other foods considered as fortification vehicles, such as dairy products and juices, is even greater (Ref. 4). Therefore, the other foods would be no more appropriate as fortification vehicles for maximizing folate intake by the target group, and yet maintaining safe consumption by nontarget groups, than cereal-grain products.

The agency notes that cereal-grain products were recommended by the Food and Nutrition Board in its 1974 report on food fortification as fortification vehicles because of the patterns of consumption of these foods. In addition, enriched cereal-grain products have a long history of being successful vehicles for improving the nutriture of the U.S. population and for reducing the risk of nutrient deficiency diseases. Thus, the agency concludes that enriched cereal-grain products are an appropriate vehicle to increase daily folate intake among women of childbearing age. In fact, the estimates that FDA developed in evaluating options for folic acid fortification demonstrate that the addition of folic acid to enriched cereal-grain products, coupled with the addition of this nutrient to breakfast cereals and dietary supplements, will help to significantly increase the daily folate intake of women in the target group (see Table 7 of 58 FR 53254 at 53295)).

Furthermore, increasing awareness of the role of folate in reducing the risk of neural tube birth defects through the use of health claims and other educational initiatives should encourage women in the target group to increase their daily folate intake by consuming folate containing foods, including enriched cereal-grain products. Consumption of cereal-grain products is also likely to be influenced by current dietary guidelines that promote increased consumption of these foods.

8. Other comments requested that FDA permit the addition of folic acid to other cereal-grain products such as whole grain flours, breads, cereals, macaroni products, rice, and grits and not just the enriched cereal-grain foods that conform to a standard of identity. The comments argued that without these products being fortified, consumers may be encouraged to eat enriched refined grains instead of their whole grain counterparts and consequently follow dietary patterns that are inconsistent with current dietary guidelines to eat whole grain products.

FDA did not propose to provide for the addition of folic acid to whole grains or products from whole grains because, traditionally, these products are not enriched. Whole grain wheat products naturally contain higher levels of the B vitamins, including folate, because the germ and bran layer are not removed when the wheat kernel is processed. FDA's standards of identity for cracked wheat, crushed wheat, and whole wheat flour, in §§ 137.190, 137.195, and 137.200, respectively, state that the proportions of the natural constituents of such wheat, other than the moisture, remain unaltered by the manufacturing process. In establishing the standards of identity for the enriched cereal-grain products, the agency's initial goal was to

restore thiamin, niacin, and riboflavin, nutrients that are removed when the bran layer and germ are removed during the processing of wheat. Subsequently, the agency required the addition of iron to the enriched grain and also provided for the optional addition of other nutrients, such as calcium and vitamin D.

The estimates that the agency has relied on in selecting a fortification level of 140 µg/100 g considered only fortification of breakfast cereals, dietary supplements, and standardized enriched cereal grain products and did not include fortification of other nonstandardized or unenriched standardized cereal-grain products. Consequently, including such foods in the fortification program could result in a daily intake of folate that is above the safe upper limit of 1 mg/day. Thus, the agency is not persuaded by the comment that other cereal-grain products should be fortified with folic acid.

With regard to the concern raised in the comment that fortification of enriched cereal grain products may encourage consumers to choose these products over their whole grain counterparts, the comment did not provide any support for its concern. The decision to fortify enriched cereal grain products at the level of 140 µg/100 g is based on current dietary consumption patterns. The agency is not persuaded by the comments that the addition of folic acid will significantly change consumption patterns of the target population. There is no evidence that women will suddenly start consuming enriched products instead of whole grain foods. In fact, one reason the agency has decided to require the fortification of enriched cereal-grain products is to enable women of childbearing age to significantly increase their daily folate intake without changing their dietary habits. Finally, the agency notes that while current dietary recommendations do encourage increased consumption of whole grain foods, they also encourage consumption of all cereal-grain products.

9. One comment expressed concern that the agency's tentative decision to fortify cereal-grain products was unfair to the cereal-grain industry because it singled out one segment of industry to address a health concern. (The agency notes that the comment was not submitted by a member of the cereal grains industry.)

As discussed in the folic acid health claims proposal, FDA considered several options that included fortification of dairy products and juices before concluding that the most appropriate option was to limit fortification to enriched cereal-grain products. Aside from the fact that these products have a long history of successful use as vehicles for increasing nutrient intake among U.S. consumers, consumption data and other relevant information reviewed by the agency show that these products are consumed routinely on a daily basis by 90 percent of women in the target group. Furthermore, some comments submitted to the docket by representatives of the cereal grains industry stated that, generally, these products can be easily fortified with folic acid. Therefore, FDA concludes that the enriched cereal-grain products are the appropriate foods for fortification, and that fortification of these products is not unfair to the industry.

C. Fortification Level

10. In the standards of identity proposal, FDA requested comments on whether the proposed fortification levels discussed for enriched cereal-grain products were appropriate. Comments responding to this issue were varied. Some comments that supported fortification of cereal-grain products stated that the proposed levels were too low to have any appreciable effect on reducing the risk of NTD's in the target population. One of these comments urged the agency to revise its proposal and require fortification at levels of at least 210 µg/100 g. However, the majority of these comments recommended that FDA require fortification of folic acid within the range of 250 to 350 µg/100 g. In support of their position, these comments contended that this range was well within limits for safety and should not mask the effects of vitamin B_{12} deficiency. One comment further argued that at a fortification level of 350 µg/100 g, 95 percent of persons in the nontarget population would not consume more than 1 mg per day. One comment recommended 400 µg/100 g for cereal-grain products. This comment argued that fortification of enriched cereal-grain products should be at the same level as dietary supplements.

However, supplemental comments submitted by a majority of the organizations supporting a higher fortification level, stated that implementing fortification at a level of at least 140 µg/100 g will constitute a critically important step forward for the health of American children. Some of these comments further stated that fortification with at least 140 µg/100 g will be the most efficient and cost-effective approach to ensuring that women of childbearing age consume the level of folic acid recommended to reduce the risk of having a neural tube defect affected pregnancy.

The agency agrees with the latter comments. As discussed in the folic acid health claims proposal (58 FR 53254 at 53279), fortification of cereal-grain products at 140 µg/100 g will produce a significant increase in daily folate intake, even for women who make food choices from the ''low'' range of the USDA Food Guide Pyramid and consume only 5 servings/day of cereal-grain products and 1 bowl of cereal containing a minimum of 100 µg of folic acid. From these sources alone, these women will consume about 320 µg of folic acid. Addition of a serving or two of vegetables, or of a serving of fruit, will provide them with a folate intake above 500 µg/day. Thus, fortification of cereal-grain products at 140 µg/100 g is an important step in assisting women of childbearing age achieve the PHS recommendation of consuming 400 µg.

However, if cereal-grain products were fortified at 350 µg/100 g, and the dietary choices indicated above were made, a ''low'' consumer would obtain 610 µg folic acid daily from these sources alone. Thus, at a fortification level of 350 µg/100 g a ''high'' consumer could reach intakes of folic acid of more than 1 mg/day from bread, noodle, rice, and pasta products alone. Additional consumption of breakfast cereals, fruits, vegetables, and a dietary supplement by ''high'' consumers could result in daily intakes of folate of about 2.5 mg/day, a level significantly above the safe upper limit of daily intake of 1 mg.

The comments supporting fortification of enriched cereal-grain products at levels above 140 µg/100 g did not provide any information to the agency that it had not considered in developing its proposed rules. Nor did the comments offer alternative fortification schemes that would allow addition of folic acid to enriched cereal-grain products at levels exceeding 140 µg/100 g yet limit the daily intake of folate to levels that are within the safe upper limit of 1 mg/day. Consequently, FDA disagrees with those comments that suggested that enriched cereal-grain products be fortified at levels of at least 210 µg/100 g. There simply is no evidence in the record that such a fortification program would keep folate intakes within the safe upper limit.

Accordingly, as proposed, the agency is requiring the addition of folic acid to enriched cereal grain products at a fortification level of 140 µg/100 g. FDA concludes that 140 µg/100 g is the maximum level of fortification of enriched cereal-grain products that would be safe for all groups.

Nonetheless, as the agency states in the final rule on the use of folic acid as a food additive, which is published elsewhere in this issue of the Federal Register, given the nature of the support for higher folic acid fortification levels in the comments, if evidence becomes available to support that there is a reasonable certainty of no harm at folate intakes above 1 mg/day, FDA would be willing to reconsider the fortification levels that it is adopting and to consider raising those levels.

11. Other comments opposed fortification at the proposed level of 140 µg/100 g on the grounds that it is too high. These comments asserted that such fortification may increase the risk of consuming folate at levels in excess of the safe upper limit of 1 mg/day in a substantial portion of the general population. Some of these comments suggested that FDA consider the lower fortification level of 70 µg/100 g in conjunction with an educational campaign that could still be effective in reducing the risk of NTD's yet not pose the risk of daily consumption of folate in excess of 1 mg/day.

In support of their position, some of these comments noted that the Food and Nutrition Board recommended the fortification of cereal-grain products at 70 µg/100 g to restore folate lost in the milling of cereal-grain products. Another comment supporting fortification at the restoration level contended that such action would permit additional restorations of nonstandardized foods such as breakfast cereals. One comment from a foreign government questioned FDA's decision to require folic acid fortification of all enriched cereal-grain products when the data do not clearly establish the effectiveness and safety of the proposed intervention program. However, the comment suggested support of the Food and Nutrition Board's 1974 proposal for cereal grain fortification, i.e., fortification with folic acid at 70 µg/100 g.

In the standards of identity proposal, FDA tentatively concluded that fortification of cereal-grain products with 140 µg/100 g folic acid was the most appropriate fortification level of the three levels analyzed to ensure that folate intakes by the target population would increase. The comments have not persuaded the agency that a fortification level of 70 µg/100 g could be as effective in assisting women in the target population to achieve the PHS recommended daily intake of 400 µg. In fact, at a fortification level of 70 µg/100 g, the estimated daily folate intake by ''low'' consumers among women of childbearing age is not likely to reach the PHS recommended levels of 400 µg/day without changes in their food selection practices (see Table 4 of 58 FR 53254 at 53292). While the agency must ensure that the use of folic acid in the food supply is safe, it must also provide as great an opportunity as is prudent and rational for all women of childbearing age to increase their intake to the recommended level. The agency concludes that a level of 140 µg/100 g is the most appropriate fortification level for enriched cereal-grain products because, based on the results of its estimated daily intakes, fortification at this level will provide daily intakes for the nontarget population that remain within the recommended safe upper limit of 1 mg/day, while providing increased intakes of folate for women in their childbearing years (see Table 7 of 58 FR 53254 at 53295).

The agency notes, however, that it has reconsidered its proposed fortification level for breakfast cereals. As fully discussed in the food additives final rule, published elsewhere in this issue of the Federal Register, FDA is permitting breakfast cereals to contain up to 400 µg of folic acid per serving. As explained in that document, the estimates for total daily folate intake that FDA presented in the folic acid health claims proposal were based on the assumption that all breakfast cereals were fortified at 400 µg/serving. Based on those estimates, daily folate intake for certain groups in the nontarget population could exceed the recommended safe upper limit of 1 mg/day. Currently, however, only about 3 to 6 percent of breakfast cereals fortify at 400 µg/serving. The agency has found no reason to expect that this percentage will change and, therefore, considers it unlikely that daily folate intake in the nontarget population will exceed 1 mg with the fortification program adopted in this final rule and in the food additives final rule.

D. Optional Versus Mandatory

Because of the increased health risk to persons with vitamin B_{12} deficiency caused by increased levels of folate intake, FDA solicited comments in the standards of identity proposal on whether the addition of folic acid to enriched cereal-grain products should be required as proposed or made optional.

12. A few comments fully supported the agency's proposal to require folic acid addition to the enriched cereal-grain products. These comments contended that required addition of folic acid was an appropriate means of increasing the daily folate intake of women in the target population. However, the majority of the comments that responded to this issue stated that fortification should be voluntary. The comments cited varied reasons in support of their position. Some comments stated that the addition of folic acid to enriched cereal-grain products should be optional pending further evidence that the benefits outweigh the risk of masking vitamin B_{12} deficiency. These comments contended that mandatory fortification of a wide variety of common products may create difficulty for people wishing to avoid folic acid. Furthermore, the comments asserted that FDA failed to establish why mandatory fortification would be necessary given that under current regulations voluntary fortification of standardized foods with folic acid is prohibited.

Other comments recommended optional fortification so that millers will not have to change their enrichment premixes for the general flour supply, thereby minimizing the costs associated with fortification, i.e., label changes, analytical testing, and inventory and supply coordination, especially for products exported to countries that do not permit folic acid fortification. The comments also stated that voluntary fortification would facilitate compliance with the various State enrichment laws.

A few comments opposed to mandatory fortification stated that FDA failed to offer information as to why voluntary fortification would not be sufficient to accomplish the public health goal of decreasing the incidence of pregnancies with neural tube birth defects. The comments urged FDA to establish a voluntary fortification program for enriched cereal-grain products and to reassess the need for a mandatory fortification in several years. One of these comments acknowledged, however, that it is difficult to predict the extent of voluntary fortification.

A small number of comments supported voluntary fortification for only the enriched noodle and macaroni products. The comments contended that voluntary compliance is consistent with FDA's current standards of identity for enriched noodle and macaroni products with regard to vitamin D, calcium, and wheat germ.

The agency does not agree with the comments that argued that the fortification of enriched cereal-grain products should be voluntary. In accepting the PHS' and Folic Acid Subcommittee's recommendation to include fortification as part of an overall plan to increase the folate nutriture of women of childbearing age, FDA has concluded that in order for a fortification program to be effective,

fortification must be mandatory for the enriched cereal-grain products. FDA is concerned that if it made fortification voluntary, and voluntary fortification were not widespread, there would be only a negligible increase in the daily folate intake of the target group, and the intent of this rulemaking would have been defeated. FDA finds that there is a public health need for women in their childbearing years to have adequate folate intake, and that the only way that it can ensure that they will have such an intake is through mandatory fortification.

FDA has traditionally used mandatory fortification to restore nutrients lost during the processing of cereal grains and thereby to address the need for reducing the risk of certain vitamin deficiency-related problems. The comments have not persuaded the agency that the same basic approach should not be applied in this case, where low folate intake represents a risk factor for a neural tube defect-affected pregnancy. USDA consumption data show that 90 percent of women of childbearing age consume cereal-grain products. Thus, mandatory fortification of cereal grains will, as stated above, increase folate intake among the target group, without requiring significant change in dietary patterns. Consequently, mandatory fortification of enriched cereal grains will help to ensure that the daily intake among the target group will reach the PHS recommended level of 400 µg. Voluntary fortification does not offer the same likelihood that folate intake will result in intakes that approach the PHS recommendation because the decision to fortify with folic acid will be at the discretion of individual manufacturers. Therefore, voluntary fortification will not adequately address the need for increased folate intake among women of childbearing age.

FDA derived the fortification levels established in this final rule based in part on a safe upper limit of 1 mg folate/day. The agency has concluded that mandatory fortification of the enriched cereal-grain products at the levels provided in this final rule is not likely to increase the risk of ''masking'' anemia in vitamin B_{12} deficient persons. Thus, the fortification program that FDA is adopting will help to ensure that the amount of folate that people in all groups of the population can reasonably be expected to consume will not exceed 1 mg/day. As discussed in the food additives final rule, the agency has examined the available data on the levels of folate that may mask anemia of vitamin B_{12} deficiency and concluded that a daily intake of up to 1 mg of folate is safe.

In response to concerns raised by millers regarding label changes, analytical testing, and inventory and supply coordination, FDA recognizes that manufacturers will need ample time to implement the changes required by this amendment of the standards of identity. As discussed below in the effective date section, FDA is permitting manufacturers time to coordinate any necessary changes that need to be made throughout the chain of food production to comply with the requirements established in this final rule as well as with the requirements set out in part 101 (21 CFR part 101).

The agency notes that manufacturers will continue to have the option of using unenriched cereal-grain products as ingredients in foods and to add enrichment nutrients to those products as they choose. Several comments from industry representatives raised a concern that the provisions in the food additive proposal would not permit addition of folic acid at the bakery site. To the contrary, as discussed in the food additives final rule, FDA will permit addition of folic acid at the bakery site as long as it is in compliance with the governing standard of identity. Consequently, manufacturers will have the same option of adding folic acid as they have with other enrichment nutrients when preparing foods that are made with unenriched cereal-grain ingredients. The agency notes, however, that any products marketed as a standardized enriched cereal-grain product will have to contain folic acid at the levels established in this final rule, and that these requirements preempt state enrichment requirements that are not identical (see section 403(a) of the act (21 U.S.C. 343(a))).

With regard to exported products, the agency recognizes that manufacturers may be required to maintain separate inventories for foreign and domestic sales. While FDA recognizes the importance of reducing trade barriers, its first obligation is to protect and promote the health of U.S. consumers. In that regard, the agency concludes that, because the fortification program adopted in this final rule is necessary to significantly reduce the incidence of neural tube defect affected pregnancies, it would not constitute an illegal trade barrier.

E. Other Issues

13. One comment from a consumer interest group recommended that if research and monitoring does not establish in the next 2 years that the risk of increasing folate intakes is significant for persons affected with vitamin B_{12} deficiency or any folate-related diseases, then FDA should increase the fortification levels in grain products or other foods and require that upper safe limits be disclosed in higher dose products. This comment urged FDA to initiate a rulemaking to restore refined grain products with most of the vitamins and minerals that are removed during milling as recommended by the Food and Nutrition Board in 1974. The comment stated its belief that such an approach would raise few safety concerns and would not be costly because manufacturers are already equipped to add nutrients to food.

FDA cannot at this time commit to increasing the levels of folic acid that may be added to food within the next several years. However, as stated above, should data become available that demonstrate that modifications need to be made to improve the effectiveness of the intervention program, and evidence be developed that the safe upper limit can be raised, FDA will decide what action is necessary. The agency notes, however, that the action it is taking in this rulemaking will more than compensate for the amount of folate lost during the milling process.

As for the comment's request that FDA initiate rulemaking to restore to refined grain products other vitamins and minerals that are removed during milling raises, the agency notes that the request issues outside the scope of this rulemaking. Therefore, no action on this request is appropriate at this time.

14. Several comments raised concern regarding the impact of the proposed regulation on foreign trade. One comment from a foreign trade association urged FDA to delay finalizing the proposed regulation to provide the International Harmonization Working Groups the opportunity to review the proposal and recommend a strategy that would serve public health goals, while achieving the spirit and intent of the North American Free Trade Agreement (NAFTA). Another comment stated that the extra costs and inherent inefficiencies of separate production runs could preclude some manufacturers from the export marketplace.

Other comments stated that the lack of consistent requirements for folic acid fortification between major trading partners, e.g., the United States and Canada, would create problems in cross-border trade and could result in higher costs for both U.S. and foreign consumers. Furthermore, these comments asserted that inconsistent requirements could reduce the competitiveness of domestic

manufacturers who export their products. Thus, the comments urged FDA to resolve the issue of exporting folic acid enriched products to foreign countries by working with foreign governments to permit export of folic acid-enriched food.

FDA recognizes that the provisions it is adopting in this final rule may be inconsistent with the fortification policies of other countries. However, as discussed above, the agency finds that the action that it is taking in this final rule is necessary to adequately protect the public health of U.S. consumers. FDA will continue to work with officials in other countries, particularly parties to NAFTA, to find ways to reduce barriers to cross-border trading of cereal-grain products and other foods.

F. Specific Standards of Identity

In this document, the agency is providing for the addition of folic acid at the level of 140 µg/100 g to the individual enriched cereal-grain products that are the subject of standards of identity. The agency described indepth the method that it used in arriving at the levels of addition for folic acid in the specific standards of identity in the standards of identity proposal. FDA will not describe that method again in this document except to the extent that clarification is warranted in response to specific comments. For a complete discussion of the basis on which FDA established the enrichment levels for the subject standards of identity, the agency refers interested persons to the standards of identity proposal (58 FR 53305 at 53307 to 53309).

1. Bakery and Wheat Flour Products

15. One comment, while supportive of the proposal to fortify cereal-grain products, suggested that a range of levels be permitted for addition of folic acid to all enriched cereal-grain products because of the inherent variation in the addition of the vitamins, the distribution of the vitamins in a food, and the analytical methodology. The comment suggested that FDA permit the addition of folic acid within a range of 24 to 35 percent over the amount established for each individual standard. For example, the comment suggested that the proposed amount of 0.7 mg/lb for enriched flour should be revised to 0.7 to 0.91 mg/lb. The comment argued that this scheme is the same as that used for enrichment in the macaroni and noodle standards and is needed for the same reasons that it is provided for in those standards.

FDA does not agree that it is necessary to provide for a range in the level of folic acid used in the production of all enriched cereal-grain products. Providing for a single level, with provision for reasonable overages within the limits of current good manufacturing practice (CGMP), has worked well with the other nutrients (thiamin, niacin, riboflavin, and iron) required to be added to enrich bread, rolls, and buns and various flour products. The provision for ''reasonable overages'' in the standards for enriched bread, rolls, and buns (§ 136.115(a)(3)) and enriched flour (§ 137.165(c)) provides manufacturers with flexibility to ensure that required levels for the added nutrients will be met, and that these levels will be maintained throughout the shelf life of the food under customary conditions of distribution and storage. While FDA is not establishing a specific upper limit for folic acid addition, the agency advises that reasonable variations for overages of folic acid will be assessed on the same basis as that for the other added nutrients in these foods. Those reasonable variations are based on a number of factors, including the technology of nutrient addition, the possibility of nutrient deterioration, the firms' quality control procedures, and appreciation by the manufacturer of these factors.

FDA acknowledges that some of the standards for enriched cereal-grain products that are the subject of this final rule specify the levels of added nutrient (thiamin, riboflavin, and iron) in terms of ranges, and FDA has continued this approach with respect to the addition of folic acid in those products. In addition, the agency notes that it received a petition (Docket No. 94P–0413/CP 1) subsequent to the issuance of the folic acid health claims proposal to amend the standards for enriched macaroni and noodle products to provide for nutrient addition in terms of a single level with provision for reasonable overages. However, FDA is not making the change to a single enrichment level in those standards at this time because, while it has reached a final decision on folic acid fortification, it has not had an opportunity to fully analyze the petition. FDA is not aware of any reason why it should delay action in the present rulemaking while it analyzes the petition. Thus, until such time as the agency rules on the petition, the standards in question will continue to provide for nutrient addition in terms of ranges.

The ranges established in those standards provide a measure of flexibility in selecting the target level when nutrients are added to foods that consist of large particles such as farina or rice, or for preparations (e.g., semolina or other ingredients) used for manufacturing enriched macaroni or noodle products. The nutrients, which usually are in the form of a fine powder, have a tendency to settle out and to make uniform blends with the cereal grains more difficult to achieve. In such instances, manufacturers, depending on their application process, may select target levels at the upper end of the range to ensure that the minimum levels established for the nutrients will be met. Thus, to enable manufacturers to adhere to procedures that will deliver the minimum level of nutrients required by the standards and to compensate for variables in the processing operations, the agency is continuing to provide for nutrient additions in terms of ranges for the other enriched foods as set forth below.

FDA also notes that the regulations for nutrition labeling in § 101.9(g)(4)(i) require that added nutrients be present in the food at levels that are at least equal to the amount declared on the label. In addition, § 101.9(g)(6) provides for reasonable overages within the limits of CGMP. Thus, the manufacturer bears the responsibility of ensuring that not only will the requirements for added nutrients in the respective standards of identity be met, but also that the content of any added nutrient is accurately declared in nutrition labeling. Therefore, consumers should receive the stated quantity of each added nutrient whether the standard provides for the added nutrient in terms of a single level or a range.

a. *Enriched flour.* No specific comments were received on the fortification of enriched flour with folic acid. Thus, as proposed, FDA is requiring that enriched flour contain 0.7 mg/lb of folic acid. FDA derived this value by adding the fortification level of 0.635 mg/lb to the Food and Nutrition Board's folate value of unfortified flour of 0.076 mg/lb, which yields 0.711 mg/lb. The agency rounded this value to 0.7 mg/lb. Accordingly, based on this calculation, FDA is amending 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.

b. *Enriched bread, rolls, and buns.* FDA is amending 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 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 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 levels of enrichment specified for the B vitamins and folic acid content are slightly lower in enriched bread products than in enriched flour to allow the bread products to be made from the standardized enriched flour without further fortification.

c. *Enriched farina.* In the standards of identity proposal, FDA proposed to establish 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.

One comment disagreed with the agency's rationale and argued that enriched farina is a different product than enriched wheat flour and therefore should not be fortified at the same level as enriched wheat flour. The comment asserted that farina is used differently than flour. For example, according to the comment, farina is often used as an ingredient in the less expensive pastas to replace the more expensive semolina. The comment pointed out that farina is also eaten as a hot cereal, and that precooked breakfast cereals are fortified with folic acid. The comment did not offer an alternative fortification level or data on which an alternative level could be based.

Because 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, and because it is the bran layer and germ that contain most of the B vitamins, including the naturally occurring folate, the amount of B vitamins lost during processing would be similar in both foods. Therefore, the agency finds that it is reasonable to fortify both flour and farina on the same basic level of 140 µg/100 g.

However, FDA acknowledges that enriched farina and enriched flour may serve different functions. Farina is often used as a substitute for a flour-containing food, e.g., as a hot cereal at breakfast, with or without other cereal-grain products being consumed at that meal, and it may be used in other foods such as pasta. However, the agency finds no basis to change the fortification level based on these possible end uses of the products because these uses are governed by other regulations. For example, when farina is used as an ingredient in the manufacture of precooked or instant breakfast cereal products, the level of enrichment is governed by the food additive regulation in § 172.345. That regulation provides that such ready-to-eat cereals may be enriched with folic acid up to 100 percent of the daily value per serving (i.e., 400 µg/serving). Neither this final rule nor the food additive final rule published elsewhere in this issue of the Federal Register, would affect the continued addition of folic acid to the precooked or ready-to-eat breakfast cereals that are manufactured with farina.

With respect to pasta products, the agency notes that the standard of identity for enriched macaroni and noodle products provides for the use of farina as an ingredient. However, the agency is not persuaded that it should adjust the fortification level for farina based on this possible use of this food. In cases where farina is used as an ingredient in an enriched macaroni or noodle product, the manufacturer has the option of adding enrichment nutrients to the farina at the flour mill or at the manufacturing facility to meet the requirements of the standard of identity for enriched macaroni or noodle products.

One comment pointed out that farina is not washed before cooking as had been noted in the proposal, and, thus, washing should not be a factor in determining appropriate fortification levels.

The agency acknowledges that current farina product labels do not suggest that enriched farina products need to be rinsed before cooking. Thus, with current technology, rinsing of the enriched farina product would not be a factor in deciding on an appropriate value for vitamin and mineral addition to farina. However, the agency notes that the proposed upper limit was not based solely on the fact that the product may be rinsed but also on the fact that it may be diluted when prepared in other recipes. The comment did not offer data to persuade the agency to deviate from the proposed upper limit of folic acid addition. Thus, as proposed, the agency is amending the standard of identity for enriched farina to provide for an upper limit for folic acid addition (0.87 mg/lb) that is approximately 25 percent higher than the 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 farina.

2. Corn and Rice Products

a. *Enriched corn grits.* No specific comments were received regarding the addition of folic acid to enriched corn grits. Thus, as proposed, FDA is amending § 137.235 to require fortification of enriched corn grits with the same level of folic acid as that established for enriched wheat flour products, such that each pound of the food would contain at least 0.7 mg of folic acid. FDA is also establishing the proposed upper limit for folic acid fortification of 1.0 mg/lb, which is approximately 50 percent higher than the 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.

The agency notes that it published a proposed rule in the Federal Register of October 13, 1995 (60 FR 53480), that would revoke the standard of identity for enriched corn grits. If comments to the proposal support revocation of this standard of identity, the provisions set forth in this final rule for enriched corn grits will also be revoked. FDA believes, however, that enriched corn grits is a widely consumed food that is likely to be eaten by women in need of additional sources of folate. Therefore, should FDA revoke this standard of identity, the agency is prepared to amend § 172.345, the food additive regulation on folic acid, to include fortified grits to the list of nonstandardized foods to which folic acid may be added.

b. *Enriched corn meals.* No specific comments were received regarding the enrichment of corn meal products with folic acid. Thus, as proposed, FDA is amending the standard of identity in § 137.260 to provide for a minimum folic acid level that is consistent with that established for enriched flour, such that each pound of the food contains 0.7 mg. Because corn meal products may be used as substitutes for wheat flour products, the agency believes, as discussed in the standards of identity proposal (58 FR 53305 at 53308), 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 establishing 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 has been 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 finds that, for the same reasons, an upper

limit on the addition of folic acid of 1.0 mg/lb is necessary.

c. *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 proposed to amend the standard of identity for enriched rice to provide for the addition of not less than 0.7 mg and not more than 1.4 mg of folic acid per pound (58 FR 53305 at 53312). The agency also noted in the standards of identity proposal that rice in the United States 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 generally bears a statement that the rice should not be rinsed before or drained after cooking, in accordance with § 137.350(c), to ensure that the rice retains the added nutrients. However, the agency stated, there is no assurance that these instructions are being 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. Rice coated with the premix is blended with unenriched rice such that the finished enriched rice product will contain the required minimum levels of added nutrients. The agency stated that the proposed range would provide flexibility in the production of the enriched rice and ensure that the food, when prepared for consumption, will contain the required minimum levels of nutrients.

16. According to comments on the standards of identity proposal, most enriched rice produced in this country is manufactured using the powder procedure to add nutrients. A comment stated that some rice processors are very concerned about the addition of an enrichment powder mix containing folic acid because folic acid could result in off colors, taste, and aromas in the enriched rice. The comment maintained that firms fear that consumers may reject the enriched rice product if it does not possess the usual white color. It further stated that processors needed additional time to conduct research on the addition of folic acid to rice.

While FDA acknowledges that the provision in the enriched rice standard for the addition of riboflavin has been stayed because of objections from the industry stating that riboflavin addition results in a yellow discoloration being imparted to the rice that is unacceptable to consumers (23 FR 1170, February 25, 1958), the agency has not received any information from rice processors that demonstrates that addition of folic acid to rice will result in off colors, taste, or aromas in the enriched rice product. Thus, as proposed, the agency is amending 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 folic acid fortification level for enriched wheat flour. FDA concludes 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 (although the Food and Nutrition Board only recommended addition at restoration levels). FDA is also establishing an upper limit for folic acid fortification of enriched rice of 1.4 mg/lb, as it has done with other enrichment nutrients added to rice. As discussed in the standards of identity proposal (58 FR 53305 at 53309), the upper level is based on the way that rice is fortified in this country.

The agency recognizes that manufacturers will need time to experiment with the addition of folic acid to their products. FDA is providing approximately 2 years from the publication date of this final rule to allow manufacturers to test their ability to comply with the new requirements and to make appropriate label changes.

17. One comment stated that, because the powder-enriched rice suffers substantial nutrient loss when it is washed (as rice is by many consumers), it is unlikely that folate intakes will increase as much as FDA estimates. The comment suggested that the agency should, consequently, increase the fortification level.

FDA disagrees with the comment. For those consumers who wish to consume ''enriched'' rice, the agency has provided requirements in the standard of identity for enriched rice to ensure delivery of the required nutrients. Section 137.350(c) requires that enrichment nutrients be present in the rice in such form and at such levels that if the enriched rice is washed, it contains not less than 85 percent of the minimum quantities of the nutrients required to be present in the enriched rice. If they are not present in such form or at such levels to comply with these minimum requirements, the label of the enriched rice must bear the statement ''to retain vitamins do not rinse before or drain after cooking'' immediately following the name of the food. In addition, the label cannot bear cooking directions that call for washing or draining the enriched rice. In the case of precooked enriched rice, the package must be labeled with directions for preparation that, if followed, will avoid washing away or draining off enrichment ingredients.

As discussed above, FDA is providing for addition of folic acid at the level of 140 µg/100 g of the enriched cereal-grain products. The agency has concluded that this fortification level is necessary to help ensure that the total consumption level will not exceed the recommended daily consumption level of 1 mg (or 1,000 µg). To minimize the potential losses in enrichment nutrients in rice, the agency had provided for a range in the levels, with an upper limit that is twice that of the minimum level required to be present in the rice. Thus, rice processors who use the powder-enrichment procedure, where nutrient losses would be expected to be greater, will be able to use a level of enrichment nutrients that makes it likely that consumers will receive the minimum levels of nutrients required to be in the food.

3. Macaroni and Noodle Products

The standards of identity for enriched macaroni products (§ 139.115), enriched nonfat milk macaroni products (§ 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.

18. One comment asserted that because of the preparation process for macaroni and noodle products, vitamin retention data are absolutely essential before any level of enrichment can be discussed. Thus, the comment recommended that FDA delay implementation of folic acid fortification of cereal-grain products until more concrete information is available on vitamin retention with cooking.

FDA is not delaying the implementation of folic acid fortification, as suggested by the comment, because of the need to increase the folic acid levels in the diets of women of childbearing age. The agency recognizes that there will be losses in the content of water soluble vitamins when the enriched macaroni and enriched noodle products are cooked in water, and that water is drained from the foods before consumption (Ref. 8). The agency also

acknowledges that data on retention of the vitamins (thiamin, niacin, and riboflavin) required to be added to enrich these foods are limited, and that it is difficult to make inferences as to the retention of added folic acid when folic acid enriched products are cooked in water, and the water is discarded. However, there are some data to suggest that the retention rates are similar.

According to a study conducted by Ranhortra, et al. (Ref. 8), on the retention rates of the thiamin, niacin, and riboflavin in three enriched pasta products (spaghetti, noodles, and macaroni), at least 50 percent (75 to 77 percent on average) of the added nutrients was retained after cooking in water and draining. This study looked at the retention of the naturally occurring folate in the pasta products, before and after cooking, and found that the retention rate was 77 to 79 percent. Based on this data, FDA does not expect that the retention rate of folic acid in these products would be significantly different from the retention rates of the other B vitamins.

FDA recognizes that, as with other grain products, manufacturers will need to conduct research on the most effective means of adding folic acid and of ensuring that the added folic acid will be available in the finished food. Such studies will need to focus on not only the method of adding the nutrient but also on the stability of the vitamin during usual conditions of distribution and storage. The agency notes that similar studies were required when FDA established requirements for the addition of the other B vitamins to enriched cereal-grain products. In addition to studies, it may be necessary for manufacturers to develop label instructions on how the product should be prepared, e.g., instructions on limiting the amount of water to be used in its preparation or cooking time, and on whether the cooked food can be rinsed without loss of nutrients before serving, to ensure maximum retention of folic acid and the added water soluble nutrients.

FDA is requiring the addition of folic acid to macaroni and noodle products in the same proportion as it is requiring such addition to enriched flour, except that the required level (expressed in terms of a range) will be approximately 25 percent higher for macaroni and noodle products than the required level of folic acid that is to be added to flour. This 25-percent increment is consistent with the requirements for 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, as proposed, FDA is requiring that the enriched macaroni and noodle products contain from 0.9 to 1.2 mg/lb of folic acid.

G. Effective Date

19. Many comments expressed concern over the statement in the standards of identity proposal that the final rule would become effective 1 year after publication. The comments stated that it would be difficult and impractical to synchronize the addition to a food of a folic acid-fortified enriched cereal- grain product with the availability of revised labels for that food that declare folic acid in the ingredient statement. These comments pointed out that enrichment nutrients are generally not added to each separately labeled product but are added to thousands of pounds of flour at the flour mill, the flour is sold to other manufacturers as an ingredient, and then this ingredient is used in many different products. Thus, the comments asserted that as a matter of economic necessity, the enrichment of all these products occurs at the same time, regardless of the availability of new labeling. One comment recommended that FDA establish an effective date of at least 2 years from the date of publication of the final rule. The comment asserted that a 2-year period would allow adequate time to incorporate changes on labels of slower moving products as well as products with higher retail turn rates. Thus, the comment continued, existing packaging inventory could be used, thereby reducing the cost impact of the regulation. Another comment suggested a ''phase-in'' period of at least 3 years or, in the alternative, an effective date consistent with the next uniform effective date, whichever is later. In support of the suggestion, the comment asserted that a ''phase-in'' period would allow label changes to take place concurrent with the folic acid addition on a product-by-product basis. In addition, the comment contended, such action would allow manufacturers to exhaust their current label inventory and reduce the economic impact of the regulation. Moreover, the comment continued, additional time is needed for analytical testing for declaration of folic acid in nutrition labeling.

FDA acknowledges the concerns raised in these comments regarding label changes that must accompany the addition of folic acid to enriched cereal-grain products and to foods in which these products are used as ingredients. FDA is persuaded by the concerns raised in the comments to establish an effective date that will provide manufacturers with time to implement the label and formulation changes required by the amendments established in this final rule. The agency agrees with the comment that suggested that FDA establish an effective date of at least 2 years from the date of publication of the final rule. A 2-year period would allow manufacturers time to exhaust current packaging inventory, add folic acid to their statement of ingredients and the nutrition facts panel as other changes are made to update package labeling, and subsequently ensure that packaging is available that accurately reflects the addition of folic acid to their products. Furthermore, the agency points out that a 2-year period is consistent with the amount of time given for implementation of the Nutrition Labeling and Education Act (NLEA) requirements. Thus, the effective date of this final rule will be January 1, 1998. The agency notes, however, that compliance with the requirements established in this final rule may begin immediately, provided that the label accurately reflects that folic acid has been added to the product. Furthermore, the agency will not object to the use of stickers to bring a product label into compliance with the ingredient labeling and nutrition labeling provisions. The agency notes, however, that unless the standardized food bears a claim about folate, the declaration of folate in the nutrition label is voluntary.

20. A few comments that raised concern about label changes that must accompany the addition of folic acid suggested that the agency permit folic acid to be added to the product without requiring declaration in the ingredient statement. One comment contended that there was no safety issue regarding folic acid that would require its declaration on the label.

Traditionally, the agency has not permitted manufacturers who change their formulas by adding or deleting ingredients to use noncompliant labels. Furthermore, as discussed in response to the previous comment, the agency is establishing an effective date in this final rule that will provide industry ample time to ensure that products enriched with folic acid are labeled in compliance with the regulations.

In response to the argument that the addition of folic acid need not be declared because it does not raise a safety issue, the agency advises that the act requires that all foods fabricated from two or more ingredients declare each of its ingredients by common or usual name in a list of ingredients. This

requirement applies without regard to whether there is a safety issue regarding the food. Consequently, the agency has not been persuaded by the comments to permit the addition of folic acid to foods without also requiring that folic acid be declared in ingredient labeling.

III. Economic Impact

FDA has examined the impacts of this final rule to require the addition of folic acid to enriched cereal-grain products that conform to a standard of identity as required by Executive Order 12866 and the Regulatory Flexibility Act. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act (Pub. L. 96–654) requires the analysis of options for regulatory relief for small businesses. FDA finds that this final rule is not a significant regulatory action as defined by Executive Order 12866. In compliance with the Regulatory Flexibility Act, the agency certifies that this final rule will not have a significant impact on a substantial number of small businesses.

On October 14, 1993 (58 FR 53305 at 53309), FDA published an economic impact analysis of the proposed requirements under the previous Executive Order (E.O. 12291). In the analysis, the agency evaluated the following regulatory options:

1. Improve dietary practices among women of childbearing age.
2. Require fortification with folic acid at 140 μg/100 g.
3. Require fortification with folic acid at: (a) A lower level, specifically 70 μg/100 g; or (b) a higher level, specifically 350 μg/100 g.

In response to the standards of identity proposal, the agency received several comments that provided information that has altered its economic impact analysis. Costs and benefits for each of the regulatory options are examined below.

A. Costs

Cost estimates are revised first for fortification at 140 μg/100 g followed by the cost estimates for fortification at 70 μg/100 g and 350 μg/100 g.

1. Require Fortification With Folic Acid at 140 μg/100 g

Costs of fortifying with folic acid at 140 μg/100 g include health costs and reformulation costs.

a. *Health costs.* Potential health costs of this regulatory option include the costs of neurologic disease associated with masking of the anemia of vitamin B_{12} deficiency. Several studies have found that folic acid can mask the anemia of vitamin B_{12} deficiency at levels as low as 250 μg/day. Although there is no scientific consensus on the percentage of diagnoses of vitamin B_{12} deficiency anemia that would be complicated by folate intake at this level, the agency has determined that adverse health effects are not significant until folate intake reaches 1 mg/day. In the proposal, FDA tentatively concluded that the 140 μg/100 g level for fortification of enriched cereal grain products was the most appropriate level based on a regulation that would have required that fortification of all breakfast cereals be limited to 100 μg folic acid/serving. This limitation was proposed under a separate food additive regulation published elsewhere in the same Federal Register (58 FR 53312). With this option, 140 μg/100 g, FDA preliminarily concluded that intake of persons in the target and nontarget populations would remain below 1 mg/day.

Comments submitted in response to the proposal to limit breakfast cereals to 100 μg folic acid/serving persuaded the agency to allow breakfast cereals to continue to contain up to 400 μg folic acid/serving. If all breakfast cereals were fortified at the level of 400 μg/serving, some high end consumers could consume more than 1 mg folate/day. However, most cereals currently are fortified at a level of 100 μg/serving (25 percent of the reference daily intake (RDI)) and only an estimated 5 percent of breakfast cereals fortify at a level of 400 μg (100 percent of the RDI).

Further, it is unlikely that manufacturers of breakfast cereals will increase the folic acid level in cereals from 100 μg/serving to 400 μg/serving. Since most breakfast cereals that contain at least 40 μg/serving (10 percent of the RDI) of folic acid can now make health claims (if all other criteria are met), manufacturers have no incentive to reformulate from 100 μg to 400 μg per serving and incur reformulation costs.

There are a number of confounding uncertainties that make it difficult to estimate the potential health costs of folic acid fortification of enriched grain products (Ref. 9). These include:

1. Current intakes estimated from food consumption survey data may underestimate actual intakes due to underreporting of food intake;
2. The folate content of foods may be underestimated due to methodologic difficulties;
3. Good data on the distribution of dietary supplement intake are not available;
4. Estimates of masking of anemia (with subsequent progression of neurologic symptoms) based on enumerating only those associated with pernicious anemia would underestimate potential adverse effects because all vitamin B_{12} deficiencies may lead to neurologic problems; and
5. It is difficult to predict effects of changes in dietary patterns that occur simultaneously with, but independently of, this regulation. Such changes may be the result of educational efforts by various organizations, physicians, and health care providers or in response to health claims.

The last factor is particularly problematic. Recent surveys have shown a growing awareness of the value of increased folate intake among both the population as a whole and, specifically, among women of childbearing age. From 1994 to 1995, awareness of the problems associated with insufficient folic acid intake grew from 28 to 44 percent among women of all ages (Ref. 10). As awareness grows, it is likely that folic acid intake will increase in the target group. In addition, new label claims allowed by the final rule for health claims on the association between folate intake and a reduced risk of NTD's are also expected to increase folic acid intake among women of childbearing age. However, the survey mentioned above also showed that such awareness is strongly positively correlated with education, so that these messages may not reach less well-educated women in the population.

In the folic acid health claims proposal, FDA tentatively found that there were several nontarget groups whose intake levels of folate may approach 1 mg/day (intakes > 800 μg/day) with a level of 140 μg/day and use of dietary supplements. These include individuals in groups including children 4 through 10 years of age and males 11 through 18, 19 through 50, and 51+ years of age. Individuals at risk of pernicious anemia include both males and females over 51 and Hispanic females ages 40 and above. The largest group at potential risk includes males over 51 who take dietary supplements. In order to be at risk of potential adverse effects from consuming greater than 1 mg folate/day individuals must: (1) Consume an excessive amount of folic acid through some combination of supplements containing folic acid and consumption of fortified enriched grain products and other products containing folic acid; and (2) have low vitamin B_{12} status or have vitamin B_{12} deficiency.

Because of the difficulties mentioned above, it is not possible to estimate the number of people in the high risk subgroup who fit all of these categories.

However, one such attempt has been made between the time of the standards of identity proposal and this final rule. In this analysis, Romano et. al. made the following assumptions:

1. The annual incidence of pernicious anemia is 9.5 to 16.7 per 100,000 persons (based on two European population-based studies);

2. With low level fortification, 5 to 10 percent of these patients would receive enough folic acid to mask the anemia of vitamin B_{12} deficiency; and

3. Between ''24 and 26 percent of patients with pernicious anemias whose anemias respond to folic acid develop neurologic signs'' (Ref. 11).

Based on these assumptions, the authors estimated that approximately 500 people per year would develop neurologic disease as a result of low level folic acid fortification. Other authors contend that this estimate may considerably understate the number of cases (Ref. 12). On the other hand, one uncertainty not acknowledged by this analysis is that this rule may create a market for cereal-grain products that are not ''enriched.'' A nonstandardized cereal-grain product could be produced that was not labeled as being enriched with folate (although it could have other vitamins and minerals added and be labeled to reflect this fact) and could be marketed to people at risk of vitamin B_{12} deficiency. If such a market developed, and at-risk persons were encouraged to consume products not enriched with folic acid, this problem might be reduced. In addition, sale to high risk subgroups of nonstandardized products such as whole wheat breads (mentioned earlier in this preamble) which do not need to be enriched, may increase as a result of this rule.

Another uncertainty that would reduce the number of cases of masked anemia, mentioned by one comment, is the percentage of cases of B_{12} deficiency that could be discovered with routine population screening. If such tests were performed proactively, B_{12} deficiencies might be identified before neurologic symptoms developed.

In addition, it is not clear whether the European population-based studies that reported the annual incidence of diagnosed pernicious anemia are relevant to the U.S. population. Some population groups in the United States (e.g., African-American women) appear to experience an earlier age-at-onset of pernicious anemia than occurs with pernicious anemia in Northern European countries, which are predominantly Caucasian populations.

Although not able to estimate an absolute number, FDA has calculated a cost per case of neurologic symptoms resulting from masking of the anemia of pernicious anemia so that a break-even point may be calculated at which point benefits would equal the costs. The cost-per-illness will be calculated using the sum of medical costs and the cost of lost utility. The majority of medical costs, which include costs for physicians, other hospital services, and drugs, are normally paid by insurance such that estimates based on willingness-to-pay to avoid death would not be likely to be included. Other utility losses, including death, pain and suffering, immobility, and lost productivity associated with morbidity, are calculated as a function of the willingness- to-pay (WTP) to avoid death. Thus, for example, each day of morbidity is a day spent in less than perfect health engendering some utility loss. That is, each day of illnesses is somewhere between a day of full utility, 1, and death, 0. Because WTP to avoid death does not include the medical expenditures mentioned above, these costs are calculated separately.

The expected utility loss estimates were calculated in the preliminary economic impact analysis (the PRIA) in the standards of identity proposal. The most common symptoms of a delay in the diagnosis of vitamin B_{12} deficiency are permanent paresthesia (numbness or tingling) in the hands or feet and ataxia (inability to coordinate voluntary muscular movements).

In the standards of identity proposal, FDA estimated the cost per case to be approximately $538,000 (Ref. 13). This estimate was calculated using weighted probabilities of a mild (95 percent) and a severe case (5 percent) and the value of expected utility loss per case of neurologic disability. For each state, mild and severe, a health status value was calculated that related the state to a day of ''perfect health''. Thus, a person with a mild case of neurologic disability is calculated to enjoy only 70 percent of the utility per day as that of a person in a perfectly healthy state. For a more severe case it would be approximately 50 percent (Ref. 14). Using the likely duration of each illness, the utility loss from a severe neurologic disability was found to be equivalent to a loss of 5.56 perfect-health years. From the value of a perfect health year, $138,889 (Ref. 14), the value of expected utility loss per case of mild neurologic disability was estimated to be $525,598. The utility loss due to severe neurologic disability was estimated in a similar fashion to be $772,598 per case. The weighted value (based on likelihood of a mild versus severe case) of a case of masked pernicious anemia leading to permanent adverse health effects was calculated as the weighted mean: $(0.95 \times 525{,}598) + (0.05 \times 772{,}598) = \$537{,}948$.

In addition to utility costs, hospital costs of neurologic effects due to pernicious anemia have been estimated by Romano et al. (Ref. 11). In this study, each neurologic case requires hospitalization once for an average duration of 16 days at $867/day. After factoring in physician services and other direct and indirect costs, the total direct outlay cost of neurologic disease as a result of folic acid fortification was estimated to be $33,000 per case (Ref. 11). Total costs per case are thus calculated to be $570,000.

However, as mentioned in Romano et al., the cost estimate may be too high because these estimates assume that all neurologic disease would be severe, and mild cases may not require hospitalization (Ref. 11). In addition, this estimate may be too high if there were routine population wide screening for vitamin B_{12} deficiency, although this is not currently occurring nor is it likely to be instituted. At the same time, however, the estimate may be too low if a case leads to later complications or to the need for lifelong skilled nursing care (Ref. 11).

These costs, lost utility and hospital costs, are not annual costs. Once someone has experienced permanent adverse health effects from masked pernicious anemia, that person ought not to be included in the costs estimated for subsequent years, since the discounted value of their permanent adverse health effects has already been calculated and attributed to the first year. Any costs in subsequent years would involve only those entering the at-risk age pool.

b. *Other health costs.* FDA is aware of the potential for other health problems resulting from increased long-term intakes of folic acid but has no data with which to quantify these costs.

c. *Reformulation costs.* Reformulation costs associated with this option were estimated in the proposal to be $27 million for the first year. The cost of adding the required folic acid is approximately $4 million per year. The cost of testing was estimated to be about $2.5 million per year and the cost of the required label changes $20 million. FDA will use these costs for this final rule as no comments were received on this part of the analysis.

In addition, some countries, such as 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. This requirement may preclude some manufacturers from the export market. None of the comments provided information that would assist in determining the costs of having different international requirements.

2. Costs of Requiring Fortification With Folic Acid at Either 70 µg/100 g or 350 µg/100 g

The total cost of the option to fortify at 70 µg/100 g in the first year was estimated in the proposal to be $25 million plus the cost of separate production runs for these products exported to and imported from certain foreign countries. For the option of fortifying with folic acid at 350 µg/100 g, the PRIA estimated a cost of $1.88 billion annually.

With the latter option, the folate intake of some consumers at risk of vitamin B_{12} deficiency (including pernicious anemia) would be raised to levels exceeding 1 mg per day. One comment to the proposal said that the estimated health costs of fortifying at this (higher) level were unrealistically high as FDA had failed to take into account that each subsequent year should only account for new cases (Ref. 11). Because of the problems with estimating numbers of people who will become ill at either level, FDA will not quantify these costs.

Reformulation costs. In the proposal, the cost of the folic acid required to fortify at 350 µg/100 g was estimated to be approximately $10 million per year. The cost of testing was estimated to be $2.5 million and the cost of the required label changes was estimated to be $20 million.

B. Benefits

1. Require Fortification with Folic Acid at 140 µg/100 g

The primary benefit of this option is a reduction in the number of infants born with NTD's each year. In addition, a possible benefit will be a reduction in cardiovascular diseases from intake of increased folate. However, there is still tremendous uncertainty with respect to the latter effect (for a more complete discussion, see folic acid food additive document published elsewhere in this Federal Register).

Based on a synthesis of information from several studies, including those which used multivitamins containing folic acid at a daily dose level of ≥ 0.4 mg, it was inferred that folic acid alone at levels of 0.4 mg per day will reduce the risk of NTD's. This conclusion was based on two studies, one from a high risk population (Hungary) with a small number of subjects that was found to be 100 percent effective and another from a study that showed zero risk reduction in a low prevalence population (California and Illinois). From these studies, the PHS estimated a reduction of 50 percent of the number of NTD's in the United States. Other studies evaluated by PHS varied in their results. A possible explanation for the lack of effectiveness was that studies were conducted in populations with a low prevalence of NTD's which may not have had a folate-related subset of NTD's.

In a study by Shaw et al., the reduction in NTD risk associated with folate intake is consistent with other studies, but the reduced risk was found to be specific to particular subsets of the population, primarily non-Hispanic women and women whose education did not exceed high school (Ref. 15). For Hispanic women, the risk reduction was approximately 10 percent. In a study by Romano et. al., the 50 percent estimate of reduced risk of NTD's was used with literature-based sensitivity limits of 67 percent (Ref. 16) and 20 percent (Refs. 11 and 17).

In the proposal, FDA estimated that under the 140 µg/100 g option, 116 NTD's per year would be prevented (50 percent reduction). Initiation of this option was also estimated to prevent an additional 25 infant deaths each year. Total benefits of this option were estimated to be between $651 and $788 million per year.

There is no consensus on the dose-response relationship between folate intake and the reduction in risk of NTD's. However, using a lower bound of 10 percent and an upper bound of a 50 percent reduction in NTD's, the estimated reductions in total cases would be between 25 (5 deaths) and 125 (27 deaths) resulting in quantified benefits ranging from $220 to $700 million.

2. Require Fortification with Folic Acid at 70 µg/100 g and 350 µg/100 g

a. *70 µg/100 g.* The benefit of requiring fortification of these products at 70 µg/100 g was estimated in the proposal to be between $326 and $394 million. Using the sensitivity limits mentioned above, 10 to 50 percent of the estimated benefits would range from $110 to $346 million.

b. *350 µg/100 g.* The benefit of requiring fortification of these products at 350 µg/100 g is estimated to be between $550 million and $1.4 billion. This option is the only option that would generate significant health costs.

C. Conclusion

In accordance with Executive Order 12866, the agency has analyzed the economic effects of this final rule and has determined that this rule, if issued, will not be an economically significant rule as defined by that order.

The cost of this final rule in the first year is estimated to be approximately $27 million which includes the cost of relabeling, testing, and fortification. In addition, there may be some health costs associated with neurologic symptoms resulting from masking the anemia of vitamin B_{12} deficiency as well as the cost of separate production runs for products exported to and imported from certain foreign countries. The cost of the proposed action in each year after the first year should be approximately 25 percent of the first year cost. The benefits are estimated to be between $220 and $700 million per year. Using a value of $570,000 per case of masked pernicious anemia resulting in neurologic damage, the break-even number of these cases at which costs would equal benefits would fall between 386 and 1,228.

Although reformulation costs of this option are approximately $27 million, the cost per firm is expected to be very small. Therefore, in accordance with the Regulatory Flexibility Act, FDA has determined that this rule will not have an adverse impact on a substantial number of small businesses.

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.

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 and Prevention, ''Recommendations for the Use of Folic Acid to Reduce the Number of Cases of Spina Bifida and Other Neural Tube Defects,'' in *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, Washington, DC, 36 pp., 1974.

4. Nationwide Food Consumption Survey, Continuing Survey of Food Intakes by Individuals: Women 19–50 Years Old and Their Children 1–5 years, 1 day, 1985; United States Department of Agriculture, Hyattsville, MD; NFCS, CSFII, Report No. 85–1, 1985.

5. 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.

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

7. Hoffpauer, D.W., ''Rice Enrichment for Today,'' *Cereal Foods World,* vol. 37, No. 10, pp. 757–759, 1992.

8. Ranhortra, G.S., J.A. Gelroth, F.A. Novak, and R.H. Matthews, ''Retention of Selected B Vitamins in Cooked Pasta Products,'' *Cereal Chemistry,* vol. 60, No. 6, pp. 476–477, 1985.

9. Crane, N. et al., ''Evaluating Food Fortification Options: General Principles Revisited with Folic Acid,'' *American Journal of Public Health,* vol. 85, No. 5, pp. 660- 666, 1995.

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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 and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR parts 136, 137, and 139 are amended as follows:

PART 136—BAKERY PRODUCTS

1. The authority citation for 21 CFR part 136 continues 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 continues 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 20 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 (mg) and not more than 2.5 mg of thiamin, not less than 1.2 mg and not more than 1.5 mg of riboflavin, not less than 16.0 mg and not more than 20.0 mg of niacin or niacinamide, not less than 0.7 mg and not more than 0.87 mg of folic acid, and not less than 13.0 mg 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 (mg) and not more than 4.0 mg of thiamin, not less than 1.2 mg and not more than 2.4 mg of riboflavin, not less than 16 mg and not more than 32 mg of niacin or niacinamide, not less than 0.7 mg and not more than 1.4 mg of folic acid, and not less than 13 mg and not more than 26 mg of iron (Fe).

* * * * *

PART 139—MACARONI AND NOODLE PRODUCTS

10. The authority citation for 21 CFR part 139 continues 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 16.5 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 (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 16.5 mg 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: February 26, 1996.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 96–5014 Filed 2–29–96; 12:03 pm]

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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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of folic acid in foods that are the subject of a standard of identity that requires the addition of folic acid; to provide for its addition to breakfast cereals on a per serving basis; to permit its use in infant formulas, medical foods, and foods for special dietary use; and to incorporate specifications for folic acid consistent with those in the Food Chemicals Codex. This action is being taken to ensure that the amount of folic acid that all segments of the population are reasonably expected to consume is safe under the Federal Food, Drug, and Cosmetics Act (the act) and to implement Public Health Service's (PHS) recommendation to increase folic acid intake by women of childbearing age, thereby reducing the risk of pregnancies affected by neural tube defects (NTD's).

DATES: Effective March 5, 1996; written objections and requests for a hearing by April 4, 1996. The Director of the Office of the Federal Register approves the incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51 of a certain publication in 21 CFR 103.35(d)(3)(v), effective March 5, 1996.

ADDRESSES: Submit written objections to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, 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, 202–418–3090.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of October 14, 1993 (58 FR 53312), FDA proposed to amend the regulation that establishes safe conditions of food use for folic acid, § 172.345 (21 CFR 172.345)). In the proposed rule, which was entitled ''Food Additives Permitted for Direct Addition to Food for Human Consumption; Folic Acid (Folacin),'' FDA said that it intended to amend § 172.345 to: (1) Set limitations on the use of folic acid on a per serving basis, in accord with the Nutrition Labeling and Education Act of 1990; (2) allow for the addition of folic acid in foods for which standards of identity exist, where such standards permit the addition of folic acid; (3) restrict to breakfast cereals the foods for which standards of identity do not exist, to which folic acid may be added; (4) continue to permit the use of folic acid in infant formulas, dietary supplements, and foods for special dietary use; and (5) incorporate specifications for folic acid consistent with those in the Food Chemicals Codex.

Interested persons were given until December 13, 1993, to comment on the proposal. FDA received 59 letters, each containing one or more comments, from consumers, members of the Folic Acid Subcommittee of FDA's Food Advisory Committee, the United States Pharmacopeial Convention, Inc., consumer interest groups, food manufacturers, trade associations, and dietary supplement manufacturers. Most comments generally supported the proposed amendments. Some comments suggested modifications of various provisions of the proposed rule or requested clarification of certain issues. A number of comments were received that were more appropriate to other dockets, and these were forwarded to the appropriate dockets (Docket Nos. 91N–100H or 91N–100S) for response. A summary of the comments and the agency's responses are presented in section II of this document.

II. Comments to the Proposal

A. Safe Upper Limit

As part of FDA's implementation of the PHS recommendation that women of childbearing age consume 400 micrograms (μg) of folic acid per day to reduce their risk of a pregnancy affected by an NTD (Ref. 1), FDA initiated this proceeding, as well as a rulemaking to authorize a health claim on the relationship between folate and NTD's and a rulemaking to require the addition of folic acid to certain standardized cereal-grains. As part of FDA's rulemaking to authorize a folate health claim, the agency found it necessary to address the issue of the safe upper limit of daily folate intake. In the health claim proceeding, FDA was confronted with all of the issues related to a safe upper limit that have been presented in this proceeding. Thus, FDA's response to the comments that addressed the safe upper limit for folic acid intake in the present rulemaking draws largely on the agency's response to similar comments as laid out in a final rule authorizing a