

**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.*

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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

health claim about the relationship of folate and neural tube defects published elsewhere in this issue of the Federal Register.

The agency's overriding goal in this food additive rulemaking is to ensure that the amount of folic acid that all segments of the population are reasonably expected to consume is safe under section 409(c)(3)(A) and (c)(5)(A) of the act (21 U.S.C. 348(c)(3)(A) and (c)(5)(A)), while concurrently aiding compliance with the PHS recommendation on folate and NTD's by increasing the folate content of the U.S. food supply.

The agency noted in the final folate health claim rule of January 6, 1993 (58 FR 2606 at 2612), and the folate health claim final rule published elsewhere in this issue of the Federal Register, that there may be risks attendant upon increased consumption of folate for some groups in the population. At the present time, the potential adverse effect for which there is the most evidence is a masking of anemia in persons with vitamin B<sub>12</sub> deficiency, while severe and irreversible neurologic damage may progress. There is currently no way to determine how many persons in the general U.S. population have undiagnosed vitamin B<sub>12</sub> deficiency, and thus, how many are potentially at risk of developing pernicious anemia. However, marginal vitamin B<sub>12</sub> nutritional status is not uncommon in the U.S. population (58 FR 53254 at 53266 to 53268), and it is observed not only in persons with pernicious anemia from an inability to absorb dietary vitamin B<sub>12</sub> but also in approximately 10 to 20 percent of elderly persons, more than 25 percent of demented patients, 15 to 20 percent of acquired immune deficiency syndrome (AIDS) patients, and 15 to 20 percent of patients with malignant diseases.

The agency further noted that other groups may be at risk from excessive intakes of folate. These other groups include pregnant women (with the potential for high levels of free folic acid affecting the embryo during early gestation) and persons on medications (the effectiveness of which could be adversely affected by high dietary folate intakes) used in the treatment of various cancers, psoriasis, rheumatoid arthritis, and bronchial asthma). Throughout its folate rulemaking proceedings, FDA evaluated the safety of high intakes of folate for all of these potentially at-risk groups. In its folate health claim final rule published elsewhere in this issue of the Federal Register, the agency described how it had reached its decision that 1 mg of total folate per day was the safe upper limit of intake.

In the folate health claim proposed rule (58 FR 53254, October 14, 1993), the agency provided data demonstrating the difficulty of concurrently achieving the PHS recommended increase in folate intake for all women of childbearing age without raising folate intakes of other segments of the population to unsafe levels. Thus, the agency recognized the significance of the proposed upper limit for daily folate intake in limiting the ability of fortification of the food supply alone to enable all women of childbearing age to achieve the PHS recommendation on folate intake. The agency also noted that there is a general paucity of evidence on the safety of daily folate intakes above 1,000 µg (1 mg). Therefore, in the folate food additive proposal, FDA specifically requested comments and data on the use of 1 mg per day total folate as a safe upper limit for establishing restrictions on food additive uses of folic acid. FDA further noted that the 1 mg daily safe upper limit for folate intake may need to be modified if data became available to support such a decision. Several comments supported FDA's tentative conclusion of 1 mg total dietary folate per day as the safe upper limit because they felt that the 1 mg per day limit is based on the best available data. As described below, other comments felt that this level was either too high or too low.

#### 1. Folate intakes of 1 mg or Less Daily

Several comments contended that current scientific knowledge is insufficient to set the safe upper limit at 1 mg folate per day, and that perhaps the safe upper limit may actually be lower than 1 mg folate per day. These comments cited published studies suggesting that 500 µg folic acid per day may mask the anemia of vitamin B<sub>12</sub> deficiency and urged that FDA set the safe upper limit below 500 µg folic acid per day. None of the commenters provided any new data to support their arguments.

FDA disagrees with those comments that contended that the safe upper limit of intake of 1 mg folate daily is too high, and that the limit should be set at a lower level. In its proposed folate health claim rule (58 FR 53254 at 53266 to 53270, October 14, 1993), FDA stated that it was aware that several published case reports suggest that there is evidence of masking of pernicious anemia in patients who consumed supplements that provided less than 1 mg folic acid daily. FDA was also aware of limited reports of masking of the anemia of vitamin B<sub>12</sub> deficiency at levels as low as 250 µg folic acid daily. These reports were the basis for the

agency's amendment, in the Federal Register of October 17, 1980, to its drug regulation on the therapeutic uses of folic acid (45 FR 69043 at 69044). In that instance, the agency required that the labeling of oral and parenteral preparations of folic acid include a "Precautions" statement that "Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations remain progressive" (see discussion in proposed health claims rule, 58 FR 53254 at 53257, October 14, 1993).

FDA, as part of its review of the scientific literature and its discussions with the Folic Acid Subcommittee, carefully considered the reports of masking at relatively low levels of folate. In its folate health claim proposal, FDA noted that the effects of intakes of less than 1 mg are infrequent, suboptimal, and less predictable than those occurring at higher intakes (58 FR 53254 at 53267, October 14, 1993).

A safe upper limit of daily folate intake of 1 mg for persons with vitamin B<sub>12</sub> deficiency was discussed by experts during a Centers for Disease Control and Prevention (CDC) workshop on surveillance for adverse effects of increased folic acid intakes. Those experts stated that there was little likelihood of problems at daily intakes lower than 1 mg (Ref. 2).

Most commenters with expertise in folate and vitamin B<sub>12</sub> metabolism and nutrition also supported a safe upper limit of 1 mg folate daily based on their scientific knowledge and clinical experiences (see folate health claim final rule published elsewhere in this issue of the Federal Register). Moreover, a safe upper limit of 1 mg folate daily is consistent with the current Reference Daily Intakes (RDI's) for folate (i.e., 400 µg daily for the general population and 800 µg daily for pregnant women, levels that were the same as the U.S. RDA's that were used as early standards for nutrition labeling (Ref. 3)) and is consistent with the 1992 PHS recommendation for women of childbearing age (Ref. 1).

Therefore, FDA concludes that for those with vitamin B<sub>12</sub> deficiency, there is little likelihood of problems if daily folate intakes are 1 mg or less. Moreover, FDA received no comments that disagreed with the agency's tentative conclusions that daily folate intakes of 1 mg or less are safe for pregnant women and for persons on medications whose effectiveness could be adversely affected by high folate intakes. Thus, FDA concludes that there is a reasonable certainty of no harm from a daily intake of up to 1 mg folate.

## 2. Folate Intakes Above 1 mg Daily

Other comments asserted that FDA's tentative conclusion of a safe upper limit of intake of 1 mg daily was too low. These comments contended that there is no evidence that folic acid intakes of 1.5 to 2 mg per day would result in any untoward effects and recommended that FDA set the safe upper limit at 1.5 to 2 mg folic acid per day. Another comment opined that setting the safe upper limit for folate intake at 1 mg per day is "arbitrary" and "paranoid." One comment claimed that the 1 mg limit is inappropriate because it is not based on substantive medical data. Several comments claimed that there is no evidence to suggest that folic acid doses at 1 mg per day are toxic. One comment argued that "[t]here is no toxicity for folic acid per se," and that "[t]he fact one mg. is needed to treat megaloblastic anemia really represents a floor. It does not speak to the intakes of Americans from food and fortification and supplements. Because Americans are laggards in their intake, a relative ceiling of 2 mgs. is not likely to be reached." This comment argued that, because the food bioavailability of folacin is fair but not excellent, fortificant and supplement intakes of folic acid are not likely to exceed one mg. None of these comments provided data to support their views.

Several comments focused on the safety of high folate intakes for pregnant women. These comments suggested that concerns about the safety of high intakes of folate in pregnant women were unfounded. In support of this contention one comment claimed that "\* \* \* millions of pregnant women have safely consumed prenatal vitamins with 1 mg of folic acid in addition to their diet over the past 15-20 years." Several comments questioned why FDA set the safe upper limit at 1 mg per day while the United Kingdom (UK) was recommending a much higher limit of 5 mg folic acid per day.

Other comments focused on FDA's concern about the absence of data on safe use for persons with marginal vitamin B<sub>12</sub> nutritional status. One comment asserted that FDA overstated the issue of the masking of B<sub>12</sub> deficiency by folate. Another comment claimed that a hematologic response to folic acid in dosages between 1 mg and 5 mg per day appears to occur in persons with clinical vitamin B<sub>12</sub> deficiency, but the frequency, magnitude, and duration of this response is unknown. The comment also stated that it is not known whether this hematological response could lead to a delay in the diagnosis of vitamin

B<sub>12</sub> deficiency. While agreeing that the masking of pernicious anemia is a concern, these comments argued that there is evidence that a substantial proportion of persons with pernicious anemia do not present with anemia before neurological symptoms. Therefore, these comments argued, these individuals would suffer the effects of undiagnosed pernicious anemia with or without folic acid supplementation. These comments did not provide any new data to support their view.

In proposing the safe upper limit at 1 mg folate per day, FDA carefully considered the available evidence on the safety for all segments of the population that might be placed at risk if folate intakes were to become excessively high. In response to the proposal, the agency did not receive any comments that provided data relating to the safety of long-term intakes of folate at levels above 1 mg per day for any of the groups considered at potential risk from increased intakes. FDA notes that both the Folic Acid Subcommittee and the Food Advisory Committee expressed concerns about the lack of information to support the safety of long-term daily intakes at levels above 1 mg (Ref. 4). The Food Advisory Committee also expressed concern about the lack of information on the size of the population potentially at risk from increased intakes of folate.

The agency is not aware of data that establish the safety of long-term intakes of folate above 1 mg per day. The absence of any data allowing systematic evaluation of intakes above this level means that potential risks and at-risk groups cannot be adequately defined or described. FDA notes that most folate and vitamin B<sub>12</sub> experts submitting comments were concerned about the lack of documentation of safety of long-term daily intakes of folate above the level of 1 mg per day. In addition to expressing safety concerns regarding those with low vitamin B<sub>12</sub> status, experts cited uncertainties about the effects of increased folate intakes by young children and the unknown physiological significance of circulating free folic acid in the blood, particularly in pregnant women. In its folate health claim proposed rule (58 FR 53254 at 53269, October 14, 1993), the agency summarized evidence from the scientific literature that high levels of free folic acid are not normally found in the circulation, and that folic acid is concentrated in crossing the placenta and accumulates in fetal tissues. At that time, the agency noted that no information was available to ascertain whether developing neural tissue is

protected from the neurotoxic effects of very high circulating levels of free folic acid. Neither these issues nor issues related to long-term folate intakes of greater than 1 mg daily by other risk groups were addressed in the comments that the agency received.

The agency finds that the comments that suggested that there is evidence of safe use of high intakes of folate by pregnant women are misleading and erroneous. The agency disagrees with comments asserting that folic acid at doses of 4 mg per day have been extensively studied in pregnant women and are without toxic effects. The agency recognizes that pregnant women take prenatal supplements that usually contain 800 µg of folic acid, and that such supplements have been in use for many years. FDA notes, however, that while there is no evidence that 800 µg of folic acid per day (i.e., the U.S. RDA level for pregnant or lactating women) is unsafe for this group, such dosages are usually taken only during the second and third trimesters of pregnancy, or during lactation, to meet specific nutritional needs for limited periods of time and are usually taken under a physician's supervision. FDA further notes that the Institute of Medicine has stated that the safety of large doses of folic acid in pregnant women has not been systematically determined (Ref. 5).

FDA also disagrees with the comments that stated that the recommendations of the government of the UK are directly relevant to inferring that 5 mg daily is a safe level of intake for pregnant women. FDA notes that these comments fail to reveal the full content of the UK recommendations (Ref. 6). The UK government made two recommendations relating daily folate intake to women of child-bearing age. The first recommendation is for health care professionals to prescribe a dietary supplement containing 4 or 5 mg (4,000 or 5,000 µg) folic acid daily until the 12th week of pregnancy to women who have already had a pregnancy affected by a neural tube birth defect and, therefore, are at a particularly high risk for another affected pregnancy. The second recommendation is that women of child-bearing age, who have not had a previous pregnancy affected by a neural tube defect and who are likely to become pregnant, should increase their intakes of folate-rich foods and take a dietary supplement containing 400 µg folic acid daily. The supplement use is recommended from the start of attempting to conceive until the 12th week of pregnancy. Clearly, the UK recommendation for women in the general population is the relevant recommendation to this rulemaking

rather than the recommendation for the use of high potency supplements, by prescription, for women at high risk of an affected pregnancy. Moreover, the UK recommendation for women in the general population is consistent with the PHS recommendation, to which FDA subscribes. Finally, and most significant to this rulemaking, the UK recommendations do not directly address the safety of fortification for the entire food supply. FDA, therefore, finds that, contrary to the suggestion in the comment, the UK's folate intake recommendations for women anticipating pregnancy, but who have not had a history of a prior affected pregnancy, are consistent with FDA's conclusions of safe intakes for pregnant women.

FDA also disagrees with the comment that asserted that folic acid at doses of 4 mg per day has been extensively studied in pregnant women, and that such doses are without toxic effects. In the only study utilizing 4 mg folic acid per day, the Medical Research Council trial, about 910 women took supplements containing 4 mg of folic acid from the time of randomization into the trial until the 12th week of pregnancy (Ref. 7). The authors of this study concluded that, although this trial had sufficient statistical power to demonstrate the efficacy of the intervention, it did not have sufficient power to answer the question of safety for public health purposes. Consequently, this study does not provide a basis on which to determine whether the chronic use of 4 mg per day of folic acid by pregnant women is safe. The agency is not aware of any other studies on the effect of daily folate intakes of 4 mg in pregnant women, or of any other data or information that would persuade the agency that 4 mg folate per day is the appropriate safe upper limit of intake for pregnant women.

FDA is also not convinced by the comments on masking of the anemia of vitamin B<sub>12</sub> deficiency that a higher value for a safe upper limit of folate intake is appropriate. As stated in the food additive proposed rule (58 FR 53312, October 14, 1993), one of the safety concerns associated with high intakes of folate is the potential for masking the anemia associated with vitamin B<sub>12</sub> deficiency which may delay accurate diagnosis and prompt treatment of this problem while neurologic damage progresses. The symptoms of vitamin B<sub>12</sub> deficiency include both hematologic and neurologic effects. While the hematologic effects of vitamin B<sub>12</sub> deficiencies are reversible, the

associated neurologic effects may be irreversible depending on how far they have progressed before detection and treatment. Any increase in the potential for masking the hematologic effects of vitamin B<sub>12</sub> deficiency may compromise prompt and effective treatment, thereby making irreversible neurologic damage more likely.

The scientific literature describing the effects of intakes of folic acid between 1 and 5 mg per day is very limited. Nonetheless, FDA disagrees with the comments that asserted that there is no evidence of untoward effects of daily folate intakes of 1.5 to 2 mg per day, and that 5 mg per day should be identified as the safe upper limit of intake.

The literature describing the effects of daily intakes of 1 to 5 mg folic acid includes three uncontrolled intervention trials involving 15 persons (Refs. 8, 9, and 10) and 16 case reports (Refs. 11, 12, 13, 14, 15, and 16). These reports represent a very small data base, with information from a total of only 31 individuals. Moreover, the agency notes that, among these data, exposures of 9 individuals to daily intakes of 1 to 5 mg folic acid lasted for less than 30 days (e.g., Refs. 9, 11, 12, and 17). These short-term reports are inadequate for assessing the safety of life-long exposures. FDA notes, however, that hematological responses that could lead to a delay in the diagnosis of vitamin B<sub>12</sub> deficiency were observed in 9 of the 16 patients (i.e., in more than 50 percent) whose daily oral intakes of folic acid were in the range of 1 to 5 mg and continued for 1 month or more (Refs. 8, 11, 12, 14, and 16). Thus, the scientific literature, although limited, shows that approximately half of the patients with pernicious anemia associated with vitamin B<sub>12</sub> deficiency responded to folate at doses between 1 and 5 mg per day when they are given the vitamin for relatively short periods of time (e.g., several months).

FDA also is not convinced by the comments that noted that adverse effects of high intakes of folate with respect to vitamin B<sub>12</sub> deficiency can be detected with clinical care and that the issue of masking of vitamin B<sub>12</sub> deficiency predated modern clinical nutrition. FDA is aware that, in many instances, the adverse effects of increased folate intake associated with the masking of the anemia of vitamin B<sub>12</sub> deficiency can be detected with clinical care but disagrees that clinical care alone is sufficient to ensure a reasonable certainty of no harm should the intake of folate exceed 1 mg folate per day. The agency notes that measurements of vitamin B<sub>12</sub> status are not performed on a routine basis by

physicians, and that there is no way to systematically determine how many people in the United States have undiagnosed vitamin B<sub>12</sub> deficiency and thus might be at risk from increased intake of folate. The agency noted in the January 6, 1993, folate health claim final rule (58 FR 2606 at 2615) that significant percentages of the elderly, demented patients, AIDS patients, and patients with malignant diseases have subnormal vitamin B<sub>12</sub> levels without having any of the classical manifestations of vitamin B<sub>12</sub> deficiency. It has been reported, in a large study (n = 548) that the prevalence of vitamin B<sub>12</sub> deficiency is greater than 12 percent among free-living elderly Americans (Ref. 18). In addition, 5 to 10 percent of all patients, regardless of age or clinical status, are found to have low serum vitamin B<sub>12</sub> levels (58 FR 2606 at 2615, January 6, 1993). Little is known about whether folate supplementation would have any adverse effect on such persons, who are far more numerous in the U.S. population than are persons with pernicious anemia.

The argument that adverse effects in persons with vitamin B<sub>12</sub>-related problems can be identified with clinical care fails to consider whether such persons, who may be unaware of their vitamin B<sub>12</sub> status, would recognize an adverse effect as being the result of increased folate intake, and whether they would seek medical attention if such an effect occurred. There is no reason to conclude that they would. Thus, the agency concludes that the argument that adverse effects in persons with vitamin B<sub>12</sub>-related problems can be identified with clinical care does not provide a sufficient basis for the agency to conclude that increasing the safe upper limit of intake provides a reasonable certainty of no harm.

In developing its proposed rules, FDA was aware of the contentious nature of the proposed 1 mg folate per day upper limit and specifically asked for data on this issue. This topic was also extensively discussed by FDA's Folic Acid Subcommittee and the full Food Advisory Committee (Refs. 4 and 19). No data were submitted in any of the comments that addressed the issue of the safety of intakes above 1 mg per day either for persons in the general population or for any of the groups identified as potentially at risk from increased folate intakes. The agency also notes that its position regarding use of 1 mg folate per day as the safe upper limit of daily intake was supported by all comments from individuals with known expertise in folate and vitamin B<sub>12</sub> metabolism and related diseases.

Because there are inadequate data and information on the safety of consuming more than 1 mg folate per day, the agency finds that it cannot conclude that there is a reasonable certainty of no harm to persons who consume more than 1 mg folate per day. In the absence of safety data on daily intakes of folate above 1 mg per day, the agency is unable to adequately define the nature, or assess the magnitude, of potential risk from increased folate intakes. Therefore, the agency concludes that, because of the lack of evidence to support the safety of intake at levels greater than 1 mg folate daily, and the potential for serious harm to some persons from such intakes, the safe upper limit for daily folate intakes is appropriately set at 1 mg, the highest intake level that meets the safety standard for food additives that there is a reasonable certainty of no harm from use of the additive.

FDA finds that 1 mg per day as the safe upper limit for folate intake is supported by: (1) The totality of the available scientific evidence and the views expressed by experts with recognized expertise in folate and vitamin B<sub>12</sub> nutrition and metabolism, that there are no data to ensure that adverse effects are not likely to occur at daily intakes above 1 mg (Refs. 2, 4, 19, and 20); (2) the PHS recommendation that folate intake of women of childbearing age should not exceed 1 mg per day (Ref. 1); and (3) the Folic Acid Subcommittee's use of 1 mg of total folate per day as a safe upper limit guide when considering fortification strategies.

The agency also is aware, however, of the rapidly evolving and potentially significant research suggesting a possible link between folate intakes and reduced risk of heart disease. The agency notes that a recent expert workshop sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health reviewed the state-of-the art science in this area (Ref. 21). The expert working group found that the currently available data, while highly suggestive of a relationship, were insufficient to demonstrate the validity of this hypothesis. Nonetheless, FDA intends to monitor and review new data and information on both the safety of daily folate intakes at levels above 1 mg daily and on the potential need for improving the folate nutritional status of large segments of the U.S. population. Should persuasive evidence emerge that provides a reasonable certainty that daily intakes of folate at higher levels are safe, the agency will take action to

modify the 1 mg per day safe upper limit for daily folate intake.

#### *B. Concurrent Vitamin B<sub>12</sub> Addition*

One comment recommended requiring the addition of vitamin B<sub>12</sub> to all foods containing added folic acid as a means to alleviate some of the concerns about the masking of the effects of vitamin B<sub>12</sub> deficiencies. Another comment claimed that many dietary supplements contained 100 percent of the RDI for vitamin B<sub>12</sub> as well as 100 percent of the RDI for folic acid and asserted that this level of vitamin B<sub>12</sub> should allay the concerns about masking vitamin B<sub>12</sub> deficiencies.

FDA is aware that very high oral doses of vitamin B<sub>12</sub> (e.g., about 1 mg; 500-times the RDI for this vitamin) have provided effective treatment for some persons with pernicious anemia (Ref. 22). These findings have led some scientists to suggest that high doses of vitamin B<sub>12</sub> could be added to foods and dietary supplements fortified with folic acid to reduce the potential for adverse effects in persons with vitamin B<sub>12</sub> deficiency.

This suggestion was discussed during a meeting on surveillance for adverse effects of increased intakes of folate organized by CDC (Ref. 2). Several experts noted that even if an individual has pernicious anemia because of vitamin B<sub>12</sub> malabsorption, they are able to absorb a small amount of oral vitamin B<sub>12</sub> (about 1 to 2 percent). Several experts, however, suggested that one possible question about using foods or food products containing added vitamin B<sub>12</sub> is that in the presence of other nutrients (e.g., vitamin C, thiamin, iron), vitamin B<sub>12</sub> may be converted into analogs, some of which may have antivitamin B<sub>12</sub> activity. The participants in this meeting noted the paucity of data about this matter. There were no conclusions or recommendations by this expert group on these issues.

In the folate health claim proposal of October 14, 1993 (58 FR 53254 at 53280), the agency discussed the issue of whether high doses of vitamin B<sub>12</sub> should be added to foods or supplements fortified with folic acid to reduce the potential for adverse effects in persons with vitamin B<sub>12</sub> deficiency. The agency requested comments, and specifically data, on the appropriateness, potential effectiveness, and safety of such fortification. The agency did not receive any data or other information on this issue.

Because data are not available that address the safety of simultaneous fortification of foods or dietary supplements with both folate and

vitamin B<sub>12</sub>, the agency cannot establish a level of oral vitamin B<sub>12</sub> that is safe for the general population, safe for persons with vitamin B<sub>12</sub>-related problems, and sufficiently high to protect persons with vitamin B<sub>12</sub>-related problems from the adverse effects of increased intakes of folate. Furthermore, FDA notes that, because difficulty in absorbing oral vitamin B<sub>12</sub> is the primary reason for inadequate vitamin B<sub>12</sub> nutrition in many persons, the amount of vitamin B<sub>12</sub> to be added would likely need to be very high, perhaps up to 500 times the RDI. Questions regarding the appropriateness, potential effectiveness, and safety of such an approach remain unanswered.

Given that vitamin B<sub>12</sub> deficiency, including pernicious anemia, is a serious condition, which if untreated can lead to irreversible neurological damage, patients with pernicious anemia, and others at risk of vitamin B<sub>12</sub> deficiency, should be diagnosed, treated, and monitored by a physician (Ref. 22). Moreover, the addition of both vitamin B<sub>12</sub> and folic acid to a food is not relevant to other potential safety issues associated with high folate intakes (e.g., high intakes in pregnant women and adverse interactions in persons on some medications). Therefore, the agency rejects the suggestion that it require the addition of vitamin B<sub>12</sub> to all foods containing added folic acid because there is not sufficient information to demonstrate that the addition of vitamin B<sub>12</sub> whenever folic acid is added will be effective for its intended purpose and will ensure the safety of the use of folic acid.

#### *C. Folate Versus Folic Acid*

Several comments supported FDA's proposal to fortify certain cereal-grain products based on a safe upper limit for total folate rather than folic acid. Some comments stated that the use of total folate as opposed to only added folic acid to set the safe upper limit of intake was advisable because this approach provides an additional safety factor. Other comments recommended that the safe upper limit should be based solely on added folic acid and not total folate intake.

In support of establishing the safe upper limit based on folic acid intakes, one comment claimed that the 1 mg limit should be based on folic acid rather than folate because the bioavailability of folate is fair but not excellent. One comment argued that using folic acid rather than folate as the benchmark for measuring the safe upper limit of total folate intake is consistent with FDA's historical treatment of the

distinction between folic acid and folate. The comment pointed out that in 1971, for example, FDA concluded that "[f]olic acid especially in doses above 1.0 mg daily may obscure pernicious anemia \* \* \*" (36 FR 6843, April 7, 1971). According to this comment, in 1979, FDA warned that for products containing 1 mg folic acid "[t]he use of folic acid for treatment of anemia without the direction of a physician may be dangerous." (44 FR 16126 at 16149, March 16, 1979.)

Several comments questioned why FDA proposed to establish the safe upper limit on a folate basis, rather than on a folic acid basis, given the fact that the human trials were run with folic acid, and there is no evidence of food folate reducing the incidence of NTD's.

Another comment recommended that the safe upper limit be established on a folic acid basis because:

\* \* \* (1) all evidence relative to the delay in diagnosis of vitamin B<sub>12</sub> deficiency at consumption levels of 1,000 mcg and above, however equivocal, derives from persons who took *folic acid* supplements orally or received folic acid parenterally and who were simultaneously consuming folates from their diets, and, (2) for years, the cut point between 'over the counter' and prescription *folic acid* supplements has been 1,000 mcg. FDA's 1971 drug use/safety regulation governing oral and parenteral usage of folic acid (36 FR 6843) stated that "folic acid especially in doses above 1.0 mg daily may obscure pernicious anemia in that hematologic remission may occur while neurological manifestations remain progressive."

As discussed previously and in the proposed rule (58 FR 53312, October 14, 1993), FDA is aware of the effect on the choice of a fortification option if the safe upper limit were established based on total folate rather than the added form of the vitamin, folic acid. FDA notes that the distinction between "synthetic folic acid," referring only to folic acid, and "folate," referring only to naturally occurring food folates, with respect to the 1 mg estimate of safe daily intake is an artificial one and is not consistent with what is known about the metabolic interrelatedness and substitutability of a variety of folate vitamin forms.

The agency acknowledges that evidence relative to the masking of the anemia of vitamin B<sub>12</sub> deficiency has been obtained from persons who consumed or were treated with synthetic folic acid. However, these individuals were also consuming unmeasured quantities of folate from foods. Thus, total daily folate exposures were unknown. The extent to which variations in background food folate intakes affected the variable responses, in terms of masking effects, cannot be

determined. The absence of data on this issue means that it is not possible to conclude that only added folic acid is responsible for any masking effects.

Moreover, the agency notes that studies in vegetarians can provide some insights into the question of whether high intakes of folates from food sources alone can have adverse effects in persons with poor vitamin B<sub>12</sub> status. Vegetarians present a model group for evaluating this question because their diets are very low in vitamin B<sub>12</sub> (because animal foods are the sole dietary source of vitamin B<sub>12</sub>) and usually very high in foods rich in folate (e.g., fruits, vegetables and legumes). Thus, vegetarians are at risk of developing vitamin B<sub>12</sub> deficiency in the presence of high folate intakes. In one study of vegetarians, the authors reported that megaloblastic anemia (i.e., the type of anemia associated with vitamin B<sub>12</sub> deficiency) is rarely encountered in Caucasian vegetarians and vegans (Ref. 23). This study also reported that the folate content of diets of vegan children aged 6 to 13 years was twice as high as that of omnivorous children aged 7 to 12 years. When infants of vegetarian mothers developed vitamin B<sub>12</sub> deficiency, they usually presented first with neurological signs and symptoms rather than anemia. Another article reported that studies conducted over several decades in vegetarian populations have all indicated that major damage to myelin synthesis (i.e., synthesis of the covering of nerves) occurs with only minor hematopoietic damage (i.e., inability to synthesize red blood cells, resulting in anemia) (Ref. 24). This report also found generally higher red cell folate in persons with greater myelin damage of the type that only vitamin B<sub>12</sub> deficiency produces than in persons with greater hematologic damage (i.e., anemia). These studies are suggestive that high food folate intakes alone can mask early hematologic symptoms of vitamin B<sub>12</sub> deficiency in vegetarians, thus, suggesting that food folates and synthetic folic acid are each capable of causing masking effects.

These observations support the view that a safe upper limit of daily intake is more accurately based on total folate intake than on just intake of synthetic (or added) folic acid. Under conditions in which vitamin B<sub>12</sub> utilization or intake is limited, either synthetic folic acid or food folate may cause masking of vitamin B<sub>12</sub>-related anemia, and these two sources appear to be additive.

FDA also disagrees with the comments that the historical concern with safety of folate intakes for drugs, as well as for FDA's food additive

regulations, was limited only to synthetic folic acid. The agency notes that the commenters' references to FDA's 1971 drug regulation in which intakes of synthetic folic acid above 1 mg daily were stated to cause masking of anemia related to vitamin B<sub>12</sub> deficiency are misleading in that they fail to note that in 1980, FDA revised the 1971 drug regulation to require a warning statement that intakes as low as 0.1 mg daily may obscure pernicious anemia (45 FR 69043 at 69044, October 17, 1980). Clearly, for the food supply, a safe upper limit of intake of 0.1 mg would be inadequate to provide the known folate nutritional requirements of the U.S. population. Thus, considerations in drugs that are intended for the treatment of persons with diagnosed diseases and health-related conditions are not necessarily directly applicable to questions of food safety.

FDA further finds that suggestions that the historical examination of food additive regulations dealt only with synthetic folic acid are not helpful. Food additive regulations on folate addition to foods necessarily specify that the added form is synthetic because that is the only form that can be a food additive. On the other hand, it is common practice when evaluating the safety of an added food ingredient to consider the safety within the context of total dietary exposures, regardless of source.

As to comments on possible differences in bioavailability between food sources and synthetic sources of folic acid and the potential of these differences to affect safety considerations, FDA discussed this issue in its proposed health claim rule (58 FR 53254 at 53273 to 53274). FDA tentatively concluded that the issue of bioavailability is complex, and that no systematic data are available on many of the factors that affect bioavailability. FDA was not aware of any meaningful way to factor bioavailability into fortification scenarios or, by extension, into evaluations of safety. FDA received no new data on this matter. Therefore, FDA has no basis on which to factor possible differences in bioavailability of synthetic, as opposed to food, folates into its determination of the safe upper limit of folate intakes.

Significantly, the use of a distinction between folic acid and folate for the purposes of establishing a safe upper limit of folate intake was not supported by any expert group that the agency consulted during this rulemaking proceeding or by comments from experts in folate and B<sub>12</sub> metabolism and related diseases (Refs. 2, 4, and 19).

Nor was it supported by any of the folate or vitamin B<sub>12</sub> experts who submitted written comments to the record. FDA received no new data or compelling arguments in this regard. Therefore, the agency concludes that the safe upper limit of daily intake should be based on total folate intake (i.e., on consumption of folate from all sources).

#### D. Breakfast Cereals

Several comments supported the proposal to limit the fortification of breakfast cereals to 100 µg per serving. One comment supported the proposed rule's distinction between the consumption of dietary supplements and breakfast cereals, noting that:

The document appropriately makes the distinction between breakfast cereal and vitamin supplements noting that some persons may consume many more than one serving of breakfast cereal per day.

In contrast, however, another comment argued that:

\* \* \* the potential for overconsumption of folic acid is greater for dietary supplements in pill/tablet/capsule form than for supplement cereals. Supplement cereal consumption is self-limiting in light of volume and caloric considerations. In contrast, smaller supplements have the potential to be consumed excessively, for example, by adults using a multivitamin/mineral product to increase vitamin C intake to combat a cold, or by children, with the potential result of iron toxicity.

Several comments recommended that currently marketed breakfast cereals containing 400 µg per serving folic acid should be allowed to continue to be formulated at this level. One breakfast cereal manufacturer argued that allowing dietary supplements to contain the full RDI level of folic acid while limiting the folic acid added to breakfast cereal to 25 percent of the RDI did not seem to be based on any scientific rationale:

If 100% RDI is a safe level for a vitamin supplement in tablet form, it surely is a safe level in a food form. In fact, food is potentially a safer alternative since the consumption is self-limiting; whereas there is greater potential for over consuming supplements in tablet form.

Several comments stated that they did not understand how FDA could reduce the level of added folic acid in breakfast cereals and still implement the PHS recommendation to have women of childbearing age consume 400 µg folic acid per day. Other comments argued that FDA should allow some breakfast cereals to contain 100 percent of the RDI for folic acid per serving as an alternative to taking dietary supplement tablets.

Still other comments argued that FDA should not make a regulatory distinction between dietary supplements in conventional and unconventional food forms. The comments asserted that both should be allowed to provide 100 percent of the daily value of folic acid.

One comment suggested that for breakfast cereals to contain 100 percent of the RDI for folic acid, they must contain 100 percent of the RDI for at least 10 vitamins for which RDI's have been determined to preserve their status as rationally balanced supplement products.

In the proposal, FDA tentatively concluded that if cereal-grain products were fortified at 140 µg folic acid per 100 g, the addition of folic acid to breakfast cereals should be limited to 100 µg folic acid per serving. FDA stated that fortification of all breakfast cereals to 400 µg folic acid per serving would result in the estimated daily intake of folate among significant portions of the population exceeding the safe upper limit of 1 mg folate per day.

FDA recognizes that fortification of some breakfast cereals at 400 µg folic acid per serving provides women of child-bearing age flexibility to meet the PHS recommendation that such women consume 400 µg of folic acid per day as a means to reduce their risk of having a pregnancy affected by an NTD. FDA emphasizes that the estimates of folate consumption presented in the health claims proposal (58 FR 53295, October 14, 1993) were based on calculations that assumed all breakfast cereals would be fortified at 0, 100 µg, or 400 µg folic acid per serving. As discussed in the proposal, most breakfast cereals are fortified at 100 µg folic acid per serving, and only 3 to 6 percent of breakfast cereals are fortified at 400 µg folic acid per serving (Nielsen Scantrack Data, A.C. Nielsen Marketing Research, Inc., Cherry Hill, New Jersey).

FDA has no basis to conclude that the current market distribution of breakfast cereals fortified at 400 µg folic acid per serving will substantially change as the result of the authorization of a health claim on the relationship of folate to NTD's. In fact, the agency notes that the health claim on the relationship between folate and NTD's may be included in the labeling of foods that are good sources of folate (40 to 76 µg folic acid per serving). Because most breakfast cereals contain folic acid at levels (100 µg folic acid per serving) that permit them to bear this health claim, there is no need for breakfast cereal manufacturers to increase their level of folic acid fortification to qualify to bear the claim.

Moreover, FDA has provided in 21 CFR 101.79(c)(2)(i)(G) that the health claim for folate and NTD's cannot state that a specified amount of folate per serving from one source is more effective in reducing the risk of NTD's than a lower amount per serving from another source. Thus, the health claim regulation provides no incentive for increasing the level of folic acid fortification in breakfast cereals.

Therefore, given the small number and limited market share of breakfast cereals that are fortified with 400 µg of folic acid per serving, the lack of incentive for there to be any significant increase in this number, and the fact that, if used appropriately, breakfast cereals can contribute to a healthful diet and provide flexibility for women in selecting foods to meet the PHS recommendation, FDA has concluded that it is not necessary to limit the addition of folic acid to breakfast cereals to 100 µg folic acid (25 percent of the RDI) per serving. FDA has determined that addition of up to 400 µg folic acid per serving in breakfast cereals is safe as long as this practice does not become widespread. FDA intends to monitor the marketplace, however, and should the proportion of breakfast cereals fortified at 400 µg folic acid change substantially, FDA may find it necessary to reconsider this conclusion.

#### E. Fruit Juice Replacements

One comment recommended that fruit juice replacements be permitted to add folic acid at 20 percent of the RDI.

FDA has considered this recommendation in light of its efforts towards implementation of the PHS recommendation and establishing safe conditions of use for folic acid.

In examining options for providing folate to women of childbearing age through food fortification, the agency considered various options including allocation of folate to products such as cereal-grain products, fruit juices, and dairy products.

In selecting foods to consider 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 (Ref. 26). The agency notes that, based on this general principle, cereal-grain products were the fortification vehicle recommended by the Food and Nutrition Board (Ref. 26).

Recent food consumption data confirm that 90 percent of women of childbearing age consume cereal-grain

products on a daily basis (Ref. 26). Therefore, all fortification options that the agency considered included fortification of cereal-grain products. Other commonly consumed food categories that may lend themselves to fortification with nutrient additives, including juices and dairy products, were also considered. Examples of dairy products and fruit juices that the agency considered for fortification included: Fluid cows' milk, reconstituted dry milk, condensed and evaporated milks, yogurts, and fruit juices such as orange, grapefruit, lemon, pineapple, apple, and grape.

FDA also included breakfast cereals in evaluating all fortification strategies because these products represent a traditional source of many nutrients, including folate, for those who consume them. Breakfast cereals are also consumed by many women of childbearing age (Ref. 27). Similarly, because approximately 30 to 40 percent of women of childbearing age use dietary supplements (Ref. 28), the agency also included the availability and continued use of dietary supplements in all fortification options.

In the agency's analyses of potential intakes from fortified foods, FDA applied different levels (70, 140, and 350 µg per 100 unit) of fortification to the broad range of food products under consideration, including certain dairy products and fruit juices.

When fortification at the lowest level, (i.e., 70 µg per unit) included fruit juices and dairy products in addition to cereal-grain products, intakes of high consumers exceeded the safe upper limit of 1 mg folate per day for most age groups. For example, fortification of cereal-grain products, fruit juices, and dairy products with 70 µg folic acid per unit, in addition to usual patterns of dietary supplement and breakfast cereal use, was estimated to result in daily folate intakes of high consumers in many groups in excess of 1 mg (58 FR 53254 at 53292, October 14, 1993).

On the other hand, as discussed more fully in the folate health claim proposal, FDA examined the effects of not including fruit juices and dairy products in its fortification model. As noted above, cereal-grain products are more widely consumed than dairy products or fruit juices by women of childbearing age. The agency examined the following fortification levels: 70, 140, or 350 µg folic acid per unit. If cereal-grain products were fortified with 70 µg folic acid per 100 g, folate intakes by adult population groups of "high consumers" would remain below 1 mg per day (58 FR 53254 at 53292, October 14, 1993). If fortification of cereal-grain products

was 140 µg per 100 g, intakes by adults 51+ years who were "high consumers" and who used supplements would approach but not exceed 1 mg folate per day. Fortification of cereal-grain products at 350 µg per 100 g could result in estimated daily intakes by "high consumers" among several sex/age groups in excess of 1 mg folate per day (58 FR 53254 at 53292, October 14, 1993).

As discussed above, FDA has concluded that 1 mg folate per day is the safe upper limit for folate intake. To ensure that the safe upper limit is not exceeded, FDA finds that folic acid fortification must be limited to the cereal-grain products that are the subject of a standard of identity that requires the addition of this substance at a level of 140 µg per 100 g. Fortification of other standardized foods with folic acid would cause the total daily folate intake of some segments of the population to exceed the safe daily intake of folate.

Because fruit juices and fruit juice replacements are not as widely consumed as cereal-grain products by women of childbearing age, they do not provide as effective a means for addressing the PHS recommendation that women of childbearing age consume 400 µg folic acid per day. Moreover, allowing their fortification in addition to the fortification of cereal-grain products would cause some members of the population to exceed the safe upper limit of intake. Therefore, FDA rejects the comments recommending that fruit juice replacements be permitted to add folic acid.

#### F. Infant Formula

One comment by a trade association representing infant formula manufacturers supported proposed § 172.345(e) which explicitly permits the addition of folic acid to infant formula, consistent with section 412(i) of the act (21 U.S.C. 350a(i)).

Another comment expressed concern that proposed § 172.345(e) would allow the addition of elevated levels of folic acid to infant formula.

FDA notes that in accordance with section 412(i) of the act, infant formulas are required to contain all essential nutrients, including folic acid. This rulemaking amends the food additive regulations to make clear that the use of folic acid in infant formula at a level necessary to provide 4 µg of folate is safe and meets the known nutrient requirements of infants when used at the required level. This level was set in accordance with the 1967 recommendations of the Committee on Nutrition of the American Academy of

Pediatrics (Ref. 29) and was incorporated into the 1980 Infant Formula Act and the 1986 Amendments to the act. Therefore, FDA concludes that addition of folic acid to infant formula at levels that comply with section 412 of the act is safe.

#### G. Dietary Supplements

In the proposal, FDA tentatively concluded that it should continue to provide for the use of folic acid in dietary supplements (58 FR 53312 at 53316, October 14, 1993). FDA received several comments supporting this tentative conclusion. Since publication of the proposal, however, the Dietary Supplement Health and Education Act of 1994 (DSHEA) was enacted. The DSHEA amended the act to exempt dietary ingredients, including vitamins, used in dietary supplements from the definition of a "food additive" (section 201(s)(6) of the act). Therefore, there is no need to provide for the use of folic acid in dietary supplements in the food additive regulations. Consequently, FDA has modified the proposed revision of § 172.345 by removing paragraph (f) and redesignating paragraph (g) as paragraph (f).

#### H. Medical Foods

A comment from a trade association that represents manufacturers of medical foods supported FDA's proposal to allow the addition of folic acid to medical foods.

FDA recognizes that it is necessary and appropriate to provide for the use of folic acid in foods that are formulated to be consumed or administered enterally under the supervision of a physician and that are intended for the specific dietary management of a disease condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation (medical foods). Therefore, FDA is providing for the use of folic acid in medical foods in § 172.345(f). In the proposal, FDA provided for medical foods as a subset of foods for special dietary use (see proposed § 172.345(g)). However, FDA has reevaluated this approach and concludes that it is more consistent with the act to provide for medical foods as a separate class of products (see section 403(r)(5)(A) of the act and compare section 411(c)(3) (21 U.S.C. 350(c)(3)) of the act with section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)).

FDA has provided for the addition of folic acid to foods for special dietary use in this final rule (§ 172.345(g)).



### I. Meal-Replacements

Several comments recommended that FDA allow the fortification of meal-replacement products with folic acid. These comments stated that weight control meal-replacement products should be allowed to be fortified with folic acid at a level based on the proportion of the total daily caloric intake that the product is intended to provide. One comment argued that meal-replacement products are unlikely to contribute to excess folic acid in the diet because their use is self-limiting. In addition, several comments argued that the addition of folic acid to meal-replacement products is consistent with the rationale used by FDA to justify the fortification of breakfast cereals, because meal-replacement products are alternatives to breakfast cereals, and like breakfast cereals, meal-replacement products are consumed typically as a single serving at the beginning of the day. In support of allowing addition of folic acid to meal-replacement products, one comment argued that these products are often consumed by women of childbearing age at breakfast in place of cereal, or they are eaten as a mid-morning snack when breakfast is skipped.

Another comment recommended that any meal-replacement products be permitted to contain up to 100 percent of the RDI per serving of folic acid. The comment argued that this level was justified because these products are usually promoted and knowingly purchased at a premium for their nutrient properties.

FDA recognizes that meal-replacement products intended to be consumed as the sole item of a meal or a diet provide persons consuming such products with essential nutrients. Moreover, folic acid fortification of such products provides an alternative to breakfast cereals and dietary supplements for women of child-bearing age that want to follow the PHS recommendation that they consume 400 µg of folic acid per day. Therefore, FDA concludes that meal-replacement products represented as a sole item of a meal or a diet may contain added folic acid.

To ensure that consumers of such meal-replacement products do not exceed the safe upper limit for folate per day, FDA has concluded that meal-replacement products that are intended to be consumed once per day may contain up to 400 µg folic acid per serving. However, to ensure that consumption of meal-replacement products does not result in folate intakes exceeding the safe upper limit of

1 mg folate per day, FDA has concluded that meal-replacement products intended to be consumed more than once per day may contain up to 200 µg folic acid per serving (§ 172.345(h)).

### J. Foodstuff Premixes

One comment requested that the agency clarify whether folic acid may be added to foodstuff premixes made with unenriched flour, but whose labeling indicates that the product contains enriched flour.

FDA recognizes that current manufacturing practices can involve the addition of nutrients, including folic acid, to premixes containing unenriched cereal-grain. FDA advises that the addition of folic acid to premixes made with unenriched cereal-grain flours, where a regulation establishing a standard of identity exists and where the standard specifically requires the addition of folic acid, is viewed by the agency as use in accordance with § 172.345(c).

### K. Specifications

Several comments requested that the proposed specifications for folic acid (§ 172.345(b)) be modified to include standards established by the United States Pharmacopeia (USP) for the use of folic acid in dietary supplements. These comments maintained that current USP and Food Chemicals Codex standards for folic acid are identical, and that including the USP requirements would help resolve any differences should USP improve the standards for folic acid. The comments noted that USP intends to establish new standards for folic acid.

As discussed previously, in response to the DSHEA, FDA has removed all references to the use of folic acid in dietary supplements from § 172.345. Establishing specifications for the use of folic acid in dietary supplements, as recommended in the comments, is beyond the scope of this rulemaking. Therefore, FDA concludes that new § 172.345(b) will specify FCC specifications for the food additive use of folic acid.

### L. Analytical Methodology

A comment noted that the current Association of Official Analytical Chemists (AOAC) method for folate quantitation in food is inadequate, and that there is a critical need for an improved method. Another comment noted that the current AOAC method is subject to considerable variability and requires 5 to 7 days to complete. The comment noted that this length of time is not practical for in-plant quality control purposes.

The agency recognizes that current methods for folate quantitation in foods may present a problem. FDA notes that folate is one of the most labile of the water-soluble vitamins, and the instability of the numerous folate forms in food has proven to be an obstacle to their quantitation.

Current methods to quantitate the level of folate in foods generally involve a two-step process consisting of extraction of folate from the food matrix followed by quantitation of folate levels. Extraction of folate from the food matrix is the most technically challenging step in the analysis. The AOAC has approved two methods for folate quantitation in food (Ref. 30). Both are microbiological assays. These assays can be completed within 72 hours after extraction of folate from the food sample.

Attempts to improve the extraction of folate from food matrices have focused on the use of a triple enzymatic digestion procedure using a broad specificity protease, an α-amylase, and chicken pancreatic conjugase. Use of the triple enzyme procedure has been found to increase measurable folate from a wide range of food matrices and has been shown to be particularly effective on cereal-grain based foods and milk and milk by-products. The triple enzyme procedure has been adapted into analysis protocols at FDA's Atlanta Center for Nutrient Analysis for the quantitation of folate in FDA's Total Diet samples (Ref. 31).

FDA scientists are studying the triple enzyme extraction procedure to identify foodstuffs for which the extraction method is most applicable. The agency also notes that a number of high pressure liquid chromatography (HPLC) methods for folate analysis and quantitation have been described in the literature. Because such HPLC methods are more rapid than the microbial methods currently in use, they offer the potential for development of a rapid folate quantitation assay for quality control purposes.

FDA will continue to work with AOAC to improve the methodology for quantitation of folate in food. The agency anticipates that the use of the triple enzyme extraction procedure and HPLC will result in advances over the current folate assays by reducing variability and assay time.

### III. 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.

#### IV. Objections

Any person who will be adversely affected by this regulation may at any time on or before April 4, 1996 file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

#### V. References

The following information has 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. Department of Health and Human Services, Public Health Service, Recommendations for the Use of Folic Acid to Reduce the Number of Cases of Spina Bifida and Other Neural Tube Defects, *Morbidity and Mortality Weekly Report* 41/No. RR-14, pp. 1-7, September 11, 1992.
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17. Davidson, L.S.P., and R.H. Girdwood, "Folic Acid as Therapeutic Agent," *British Medical Journal*, 1:587-591, 1947.
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19. Transcript of meeting of Folic Acid Subcommittee/Food Advisory Committee Meeting, Arlington, VA, April 15-16, 1993.
20. Briefing material, Folic Acid Subcommittee Meeting, April 15, 1993.
21. National Heart, Lung, and Blood Institute of the National Institutes of Health Workshop.
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#### List of Subjects in 21 CFR Part 172

Food additives, Incorporation by Reference, Reporting and recordkeeping requirements.

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

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

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

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

2. Section 172.345 is revised to read as follows:

**§ 172.345 Folic acid (folacin).**

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

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

(b) Folic acid meets the specifications of the "Food Chemicals Codex," 3d ed. (1981), pp. 125 to 126, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51.

Copies may be obtained from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(c) Folic acid may be added to foods subject to a standard of identity established under section 401 of the Federal Food, Drug, and Cosmetic Act (the act) when the standard of identity specifically provides for the addition of folic acid.

(d) Folic acid may be added, at levels not to exceed 400 micrograms ( $\mu\text{g}$ ) per serving, to breakfast cereals, as defined under § 170.3(n)(4) of this chapter.

(e) Folic acid may be added to infant formula in accordance with section 412(i)(1) of the act or with regulations issued under section 412(i)(2) of the act which are codified in § 107.100 of this chapter.

(f) Folic acid may be added to a medical food, as defined in section

5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)), at levels not to exceed the amount necessary to meet the distinctive nutritional requirements of the disease or condition for which the food is formulated.

(g) Folic acid may be added to food for special dietary use at levels not to exceed the amount necessary to meet the special dietary needs for which the food is formulated.

(h) Folic acid may be added to foods represented as meal-replacement products, in amounts not to exceed:

(1) Four hundred  $\mu\text{g}$  per serving if the food is a meal-replacement that is represented for use once per day; or

(2) Two hundred  $\mu\text{g}$  per serving if the food is a meal-replacement that is represented for use more than once per day.

Dated: February 28, 1996.

David A. Kessler,

*Commissioner of Food and Drugs.*

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