21 CFR Part 101

[Docket No. 91N-0100]

RIN 0905-AB67

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing not to authorize the use on the label and labeling of foods, including dietary supplements, of health claims relating to an association between folic acid and reduction in risk of neural tube defects. FDA has reviewed the scientific data in conformity with the requirements of the Nutrition Labeling and Education Act (the 1990 amendments) and has tentatively concluded that there is not a sufficient basis to support the use of health claims relating to this topic. FDA also reviewed recently published results of a large intervention trial of effects of supplements containing very high levels of folic acid in women who, because of histories of neural tube defect-complicated pregnancies, were at high risk of recurrences of these specific birth defects in subsequent pregnancies. Currently there is not significant agreement among qualified experts that intakes of folic acid lower than those studied in this intervention trial will have the same effect as that observed with very high intakes.

Additionally, at this time, there is no significant agreement among qualified experts that folic acid supplementation of women at much lower risk of occurrence of neural tube defect-affected pregnancies will reduce the risk of such a complication. However, the results of the recently published intervention trial are causing some qualified experts to reevaluate the preexisting evidence. FDA will consider all developments in this regard and reflect such developments in any final rule that it issues. FDA has tentatively concluded that claims on foods, including dietary supplements, relating to folic acid and reduction in risk of neural tube birth defects are not justified.

DATES: Written comments by [January 27, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the Nutrition Labeling and Education Act of 1990.

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

FOR FURTHER INFORMATION CONTACT: Jeanne I. Rader, Center for Food Safety and Applied Nutrition (HFF-268), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-6067.

SUPPLEMENTARY INFORMATION:

I. Background

A. The 1990 Amendments

On November 8, 1990, the President signed into law the 1990 amendments (Pub. L. 101-535), which amended the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorize the Secretary of Health and Human Services (the Secretary), and FDA by delegation, to issue regulations authorizing nutrient content and health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under the act (21 U.S.C. 343(r)(1)(B)).

Published elsewhere in this issue of the **Federal Register** is a proposed rule to establish general requirements pertaining to the use of health claims on food labels and in labeling that characterize the relationship of nutrients, including vitamins and minerals, herbs, or other nutritional substances (referred to generally as "substances") to a disease or health-related condition. In this document entitled "Food Labeling: General Requirements for Health Claims for Food: Proposed Rule (the companion document), "FDA has tentatively concluded that such claims would only be justified for substances in dietary supplements as well as in conventional foods if the totality of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner that is consistent with generally recognized scientific procedures and principles) supports a claim; and if there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims about such support.

The 1990 amendments also require (section 3 (b)(1)(A)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x)), that within 12 months of enactment, the Secretary issue proposed regulations to implement section 403(r) of the act, and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including folic acid and neural tube defects, meet the requirements of the act. In this document, the agency considers whether a claim on food or food products, including conventional foods and dietary supplements, on the relationship between folic acid and neural tube defects would be justified under the standard proposed in the companion document.

FDA has followed the general concepts and criteria proposed in the companion document in considering whether to propose to authorize the use on the labels and labeling of food of health claims for folic acid and neural tube defects. In the companion document, FDA has proposed that, in evaluating whether support exists for a health claim, it will consider the levels and safety of a nutrient within the context of its use in the daily diet. Before a health claim for a particular nutrient will be authorized, it is necessary that the nutrient be safe and lawful for use in food at the level found to have an effect on a disease or health condition.

The topic of folic acid and neural tube defects involves a substance which has recognized uses both as a component of food and of drugs. The agency has looked at all data relevant to this topic whether the data involved tests at dietary levels or at therapeutic levels. The agency thought this necessary to ensure the completeness of its review. However, the agency emphasizes that this proposal is only about whether a claim has been justified for folic acid on food. A component of food must be safe in the context of the daily diet. On the other hand, drugs may be used even if they present questions of safety to the general population, and even to the population being treated, on the basis that there is a benefit from its use that outweighs the potential risk.

B. Folic Acid and Neural Tube Defects: Public Health Aspects

Congenital malformations are structural abnormalities that are present at birth. Several specific malformations of the central nervous system (CNS) are referred to as "neural tube defects" because the brain and spinal cord develop within the neural tube. The neural tube forms early in fetal life, between the 18th and 20th days of pregnancy, and closes between the 24th and 27th days of pregnancy. Neural tube defects include a wide range of abnormalities of the CNS. They may be isolated malformations or may occur in association with other nonneural congenital malformations.

Anencephalus and spina bifida account for about 90 percent of neural tube defects (Ref. 1). Anencephalus is an abnormality in which there is a virtual absence of the forebrain and skull. Most anencephalic infants are stillborn. Live-born anencephalic infants may survive for only a few days. Spina bifida is a general term describing various developmental abnormalities characterized by defective closure of the bony encasement (the vertebrae) of the spinal cord. The spinal cord and nervous system tissues may protrude through openings resulting from failure of the vertebrae to form normally. Infants born with spina bifida may lack normal function below the level of the defect because of damage to specific nerves.

Anencephalus and spina bifida are more common in Caucasian populations than in other racial groups. Reports of prevalence per 1,000 births in Caucasian populations have yielded the following estimates for anencephalus and spina bifida, respectively: Wales, 3.6, 4.1; Scotland (Glasgow), 2.8, 2.8; Northern Ireland, 3.1, 3.3; Hungary (Budapest), 1.1, 1.6 (Ref. 2). In contrast, prevalence of anencephalus and spina bifida in Japan has been reported to be 0.43 and 0.08, respectively, per 1,000 births (Ref. 2). Rates of neural tube defects in hospital series in northern China, however, are among the highest yet reported and range between 5 and 13 per 1,000 births (Ref. 2a).

The incidence rate of neural tube defects at birth has been reported to vary a wide range of factors, including genetics, geography, socioeconomic status, maternal birth cohort, month of conception, race, nutrition, and maternal health including maternal age and reproductive history. Epidemiologic evidence indicates that there is a strong genetic component involved in neural tube defects (Ref. 3). This genetic component is well-recognized, and familial recurrence patterns are the single greatest risk factor for neural tube defects, although studies in humans have not as yet localized the responsible genes. Carriership for inborn (genetic) errors of homocysteine (a metabolic product of methionine; an intermediate in the synthesis of cystine) metabolism has recently been proposed as a risk factor for having an infant with a neural tube defect (Ref. 4).

In the United States, neural tube defects affect approximately 1 in 1,000 infants at birth (Ref. 2) (i.e., the occurrence rate is approximately 0.1 percent). Occurrence rates are about 4 in 10,000 infants at birth (0.04 percent) in low-risk areas. For example, within the United States, the available hospital data and community surveys show that rates are highest in the northeast and lowest in the west, with anencephalus rates of about 0.5 per 1,000 (0.05 percent) in Iowa and Los Angeles (Ref. 2).

The number of first occurrences of neural tube defects exceeds the number of recurrent events. The great majority of families having an anencephalic or spina bifida infant will experience only one such affected pregnancy. A small minority of about 5 percent, however, will have more than one affected infant (i.e., a recurrence) (Ref. 5). Thus, the risk of having an infant with a neural tube defect is much higher among women who have had a previous pregnancy complicated by a neural tube defect than among women who have not had such a complication. Among women with histories of previous neural tube defect-complicated pregnancies, rates for recurrence of such defects have been estimated to be as high as 2 to 10 percent compared to occurrence rates of about 0.1 percent in the general population (Ref. 3). The pattern of recurrence of these defects is that expected of a polygenic (i.e., caused by several genes) trait. Data from the most recent report of the National Birth Defects Monitoring Program of the Centers for Disease Control (CDC) show decreasing trends for anencephalus and spina bifida between 1979 and 1987 in the United States (Ref. 6).

The striking geographical variations in prevalence at birth of anencephalus and spina bifida have not been adequately explained. For example, the range of prevalence rates in the United States and Canada is very large, with the highest prevalence rates found in the eastern portions of both countries. Additionally, the relatively low prevalence rates in western Canada (British Columbia) have been stable over time, in contrast to the highe rates in eastern Canada which have shown large secular variations similar to trends in the British Isles (Ref. 2). These observations suggest the action of fairly stable genetic factors, with higher but less stable rates possibly caused by the interaction of varying environmental factors with stable genetic factors (Ref. 2).

Maternal health, for example, febrile illness (Refs. 1, 7, and 8) and maternal use of certain drugs also have an effect on the development of neural tube defects. There is an increased incidence rate of malformations (including neural tube defects) among infants of diabetic mothers (Ref. 9). Therapeutic use of valproic acid, an anticonvulsant drug, is associated with markedly increased risk of neural tube defects (Ref. 10, 11, 12, and 13).

Epidemiologic studies suggest that factors associated with acute or chronic poverty also play a role in modifying the incidence rates of neural tube defects. Observational studies in humans suggest that poor maternal nutrition, which is among a number of factors associated with poverty, may increase the risk of neural tube defects. For example, in the United Kingdom, mean values for blood levels of a number of vitamins have been reported to be most satisfactory in women in the highest social classes (Ref. 14). Blood concentrations of several vitamins were reported to be lower on average in women who subsequently gave birth to infants with neural tube defects than in women who did not (Ref. 14). Such evidence is relatively nonspecific, however, since dietary deficiency of one nutrient is frequently correlated with deficiencies of other nutrients.

Maternal nutritional status around the time of conception (the "periconceptional period") is of special concern because, as stated above, the neural tube forms and closes very early in embryogenesis (Ref. 3). The periconceptional period, however, has not been precisely defined. The National Academy of Sciences (NAS) suggested in its 1990 report that this period or interval extends from 1 to 3 months before conception to week 6 of gestation (Ref. 3).

The hypothesis that nutritional factors might be involved in causing some human neural tube defects is based on findings from several types of studies. These include: (1) animal studies in which deficiencies of some vitamins during pregnancy (such as vitamin B_{12}, vitamin B_6 and pantothenic acid) produced a variety of fetal abnormalities, including neural tube defects (Ref. 1); (2) epidemiology studies of neural tube defects in humans that suggest a link with nutrition because of variations in prevalence with social class, dietary habits, and season (Ref. 9); and (3) clinical observations of congenital malformations including neural tube defects in offspring of women who were given an antifolate drug (a drug which alters folic acid status by interfering with absorption, metabolism, or functions of the vitamin) to test its efficacy as an abortifacient.

Among the nutrients that may have a role in development of neural tube defects, folic acid has received the greatest amount of attention because of observational studies in humans and because of the well-recognized roles of this vitamin in cell division and growth.

Folic acid is essential for humans. Folate compounds occurring naturally in foods are in a reduced pteroyl form. Folates occurring in plant and animal cells contain two to eight additional glutamic acid molecules which are linked to the glutamate end of the folate molecule. The folylpolyglutamates which occur in foods are broken down to the monoglutamate forms in the intestine. Commercially available folic acid (pteroylglutamate) is in an oxidized state relative to its occurrence in foods.

Insufficient quantities of folate in the diet lead to impaired cell multiplication and alterations in protein synthesis. These effects are most noticeable in rapidly growing tissues. Abnormalities of rapidly dividing cell populations (for example, those of the gastrointestinal tract and bone marrow) are among the most notable results of folate deficiency because of the essentiality of this vitamin for synthesis of deoxyribonucleic acid.

Determinations of folate in serum and in red blood cells are commonly used to assess folate status. Red blood cell folate concentrations are considered to be a better index of long-term folate status than are measurements of serum folate. Folic acid administered orally is effective for the treatment of megaloblastic anemias of nutritional origin, and those that may develop in women during pregnancy, and those that may develop in infants and children. Pregnancy increases the need for folic acid among other nutrients because of the need of the mother to maintain adequate nutrition and to meet the nutritional requirements of the rapidly developing fetus.

The Medical Research Council of the United Kingdom recently reported (Ref. 15) that periconceptional supplementation of women at high risk of recurrence of neural tube defect-complicated pregnancies with 4 milligrams (mg) folic acid per day significantly reduced the rate of such recurrences. In response, CDC issued guidelines (see section II A. below) for physician-directed use of high doses of folic acid by women who, because of histories of neural tube defect-complicated pregnancies, are at high risk of recurrences of these specific birth defects in subsequent pregnancies (Ref. 16). FDA regards the marketing of folic acid at the dosage and for the use recommended in the interim CDC guidelines (Ref. 16) to require an approved new drug application (NDA). No NDA has been approved by FDA for folic acid for prevention of neural tube defects.

C. Folic Acid: Regulatory History

FDA has promulgated regulations describing uses of folic acid as a dietary supplement and as a drug. These designations are dependent on the intended uses of this vitamin. Section 172.345 (21 CFR 172.345) provides for the use of folic acid in dietary supplement preparations. Preparations containing folic acid in excess of the permitted food additive level (see below) are regulated as drugs and are available with a prescription.

FDA evaluated the use of folic acid as a drug in the **Federal Register** of April 9, 1971 (36 FR 6843) in response to reports received from NAS on the therapeutic uses of folic acid. The agency concluded that folic acid administered orally or parenterally is effective for the treatment of megaloblastic anemias of tropical and nontropical sprue, those of nutritional origin, and those which may occur during pregnancy, infancy, and childhood (36 FR 6843). The agency found that administration of folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient (36 FR 6843) because such treatment may mask the symptoms of vitamin B_{12} deficiency. FDA also concluded that there is no evidence that doses of folic acid greater than 1 mg daily have greater efficacy in treatment of megaloblastic anemias than do those of 1 mg (36 FR 6843).

Folic acid is an approved food additive subject to the limitations on use set forth in the food additive regulation § 172.345. Folic acid (folacin) may be safely added to a food for its vitamin properties, provided the maximum intake of the food as may be consumed during a period of 1 day, or as directed for use in the case of a dietary supplement, will not result in daily ingestion of the additive in excess of 0.4 mg for foods labeled without reference to age or physiologic state. When age or the conditions of pregnancy or lactation are specified, the regulation provides that the level of ingestion shall not exceed 0.1 mg for infants, 0.3 mg for children under 4 years of age, 0.4 mg for adults and children 4 or more years of age, and 0.8 mg for pregnant or lactating women (21 CFR 172.345).

D. Evidence Considered in Reaching the Decision

The agency has reviewed all relevant scientific evidence on folic acid and neural tube defects. The scientific evidence reviewed by the agency included all human studies considered in "The Surgeon General's Report on Nutrition and Health" (Ref. 21), and the United States Department of Agriculture's and the Department of Health and Human Services' "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 22). The other reviews conducted by widely recognized scientific bodies that FDA considered were NAS' "Diet and Health" (Ref. 23), the National Research Council's "Recommended Dietary Allowances" (Ref. 24), the NAS' "Nutrition During Pregnancy" (Ref. 3), and the Life Sciences Research Office's (LSRO) "Folic Acid and Neural Tube Defects" (Ref. 25). The agency updated the conclusions reached by these documents by reviewing all human studies that appeared in the literature subsequent to these documents and all new review articles. The agency also considered the results of animal studies to the extent that they clarified human studies or suggested possible mechanisms of action.

To assure that its review of relevant evidence was complete, FDA requested, in the **Federal Register** of March 28, 1991 (56 FR 12932), scientific data and information on the 10 specific topic areas identified in section 3(b)(1)(A) of the 1990 amendments. The topic of folic acid and neural tube defects was among the 10 subjects on which the agency requested information.

E. Comments in Response to FDA Request for Scientific Data and Information

In response to the March 28, 1991 notice in the **Federal Register**, FDA received 12 comments to the docket for folic acid and neural tube defects from manufacturers and suppliers of vitamins to the food and dietary supplement industries, trade associations of nutritional supplement manufacturers, national professional organizations of nutritionists and public health nutrition directors, and the government of Canada. The comments dealt with the issue of folic acid and neural tube defects as well as with the goals and requirements of the 1990 amendments in general. FDA reviewed all of the documents, including letters, press releases, scientific articles, review articles, and recommendations included in submissions that it received. The data submitted in scientific articles were included in the agency's review of the scientific literature.

Among the comments received were three from manufacturers and suppliers of vitamins and two from trade associations of nutritional supplement manufacturers. The submissions from these groups stated that there is sufficient evidence to provide claims for

periconceptional multivitamin (including folic acid) supplementation for reduction in risk of neural tube defects and possibly cleft lip/palate. One comment recommended a Recommended Dietary Allowance (RDA) RDA-level multivitamin supplement for all women of child-bearing age.

One comment from a manufacturer of vitamins recommended multivitamin supplementation for 3 months preceding through 3 months following conception. The comment pointed to several reasons for supplementation during this interval including: (a) The available data; (b) almost risk-free nature of such supplementation; (c) low cost of such supplementation; and (d) economic aspects of care and treatment of infants born with severe birth defects. Another comment from a trade association of nutritional supplement manufacturers stated that there is no risk associated with use of a multivitamin supplement with folic acid with or without minerals by women contemplating pregnancy.

The "almost risk-free" or "no risk" rationale does not qualify as a basis for a health claim. The 1990 amendments require that a health claim be based on the totality of all available scientific evidence and significant agreement among experts qualified by training and experience to evaluate such evidence. Thus, the agency rejects the concept of "almost risk-free" or "no risk" as justification for a health claim because it is inconsistent with requirements of the 1990 amendments.

FDA disagrees with statements regarding the "low cost of such supplementation." Practical difficulties of providing folic acid supplements to all women before pregnancy, and particularly to women before their first pregnancies, are formidable and would be of substantial cost. These factors are important in this instance because there are no data demonstrating benefits to be derived from widespread supplementation of all women of child-bearing age.

The comments also included a number of references relating to effects of anticonvulsant drugs on folic acid status. These articles were included to demonstrate that certain subgroups in the population may require supplemental folic acid as a result of medications that they are taking.

Comments were received from two national professional organizations of nutritionists and public health nutrition directors. These comments advised a cautious approach to the use of health claims on foods and supplements with particular attention to avenues by which such claims might be abused or misinterpreted by the general public. The comments recommended that scientific agreement should be the cornerstone for the use of health claims, and that FDA consider data submitted in the context of meeting dietary requirements through intake of food. Some concern was expressed that the 1990 amendments allowed so many potential topics as candidates for possible health claims.

The government of Canada submitted information that it considered helpful in the context of increased harmonization of regulations or standards affecting trade in specific products. The Director General, Food Directorate, Health and Welfare Canada, wrote to the agency that health claims or messages regarding neural tube defects would likely result in a food product being classified as a drug in Canada by virtue of the definition of "drug" embodied in the Canadian Food and Drugs Act.

The official position of Canada on the relationship of diet and nutrients to disease and the metabolic effects of nutrients is stated in the volume *Nutrition Recommendations, the Report of the Scientific Review Committee—1990* (Ref. 17). In sections relating to folic acid, this report noted that there was particular interest in folate intake before conception and in early pregnancy in view of a reported possible relationship between folate and occurrence of neural tube defects. The report noted that intervention trials carried out in the United Kingdom (Refs. 18, 19, and 20) have been criticized, and that a large controlled trial on prepregnancy supplementation was in progress at the time of the report (Ref. 20). The report does not contain a recommendation for periconceptional supplementation with folic acid (Ref. 17).

II. Review of the Scientific Evidence

A. Federal Government Documents and Statements

In 1988, "The Surgeon General's Report on Nutrition and Health" (Ref. 21) considered the role of dietary factors in maternal health. This report reviewed the results of clinical trials in the United Kingdom in which folate and multivitamin supplements were used in attempts to reduce the risk of recurrence of neural tube defects in infants born to women who had previously had a pregnancy complicated by a neural tube defect. The Surgeon General's Report, citing extensive commentaries (Ref. 26), reported that these trials were poorly controlled for maternal diets and were methodologically flawed by poor compliance, questionable exclusion of eligible participants and recruiting bias (Ref. 21). The report did not make a recommendation with respect to folic acid supplementation before or during pregnancy (Ref. 21).

The U.S. Department of Agriculture and the Department of Health and Human Services, in "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 22), did not discuss any scientific evidence on a relationship between folic acid and neural tube defects. The target populations for these guidelines are healthy Americans and not those persons in the population with chronic diseases or those at high risk of specific diseases. In 1988, the CDC reviewed methodological concerns about case-control studies, and stated that the available evidence was insufficient to recommend multivitamin supplementation in the United States to prevent neural tube defects (Ref. 27).

Following the recent publication of the results of the Medical Research Council (United Kingdom) Vitamin Trial (Ref. 15), the CDC published guidelines, reprinted near the end of this preamble, recommending that a woman who has had a fetus or infant with a neural tube defect should consult with her physician at least 4 weeks before becoming pregnant and should take, under a physician's guidance, 4 mg folic acid per day through the first trimester of pregnancy (Ref. 16).

The CDC stated that these guidelines are not intended for women who have never had a neural tube defect-affected pregnancy, for relatives of women who have had an infant or fetus with a neural tube defect, for women who themselves have spina bifida, or for women who take the anticonvulsant drug valproic acid, a known cause of spina bifida (Ref. 16).

The National Institutes of Health's National Institute of Child Health and Human Development does not have a public policy on this issue (Ref. 28).

B. Other Documents and Statements

The NAS' 1989 report "Diet and Health" did not contain any general recommendation for periconceptional supplementation with folic acid (Ref. 23). No recommendations for periconceptional folic acid supplementation to reduce the risk of birth defects were made in the National Research Council's 1989 edition of "Recommended Dietary Allowances" (Ref. 24). In 1990, NAS reviewed the topic of periconceptional vitamin supplementation and neural tube defects in its report "Nutrition During Pregnancy" (Ref. 3). NAS reviewed studies of vitamin supplementation during the periconceptional period, case-

control and cohort studies of periconceptional multivitamin use, results of laboratory assessments of maternal vitamin status, and studies in animal model systems (Ref. 3). NAS found severe limitations in the available evidence including:

(1) Inconsistency of data associating multivitamin or folate use with protection against neural tube defect pregnancies; and

(2) Evidence that in animal model systems, deficiency of nutrients other than folic acid produced lesions similar to human neural tube defects (Ref. 3).

NAS concluded that the scientific evidence derived from various types of human studies and from animal studies does not provide a sufficient basis for making broad recommendations concerning the periconceptional use of vitamins and minerals for the prevention of neural tube defects (Ref. 3).

LSRO of the Federation of American Societies for Experimental Biology also reviewed the scientific literature regarding folic acid and neural tube defects (Ref. 25). The LSRO report concluded that there is evidence that women who take folic acid or folic acid-containing vitamin supplements during the periconceptional period have a lower risk of having infants with neural tube defects. In reaching this conclusion, LSRO was frequently inconsistent in its review of the relevant human studies and in the conclusions drawn from the results of the studies. The report also failed to focus on the specific relationship of folic acid to neural tube defects and on the significant differences in risk of occurrence versus recurrence of neural tube defect-complicated pregnancies. LSRO also concluded that women who have given birth to an infant with a neural tube defect will have a lower risk of bearing another child with a similar defect in a subsequent pregnancy if they take a folic acid supplement during the periconceptional period.

Thus, the authors of Federal government documents and other authoritative reports (with the exception of the LSRO report noted above) from panels of experts who conducted indepth reviews of the effects of periconceptional use of vitamins and minerals found that the available evidence did not provide a basis on which to conclude that the periconceptional use of vitamins and minerals will reduce the risk of neural tube defects among women in the general United States population.

Several professional health organizations were also contacted to determine whether they have policies on periconceptional supplementation with folic acid and neural tube defects at this time. The American College of Obstetricians and Gynecologists does not provide any specific recommendations to their fellows on preconceptional folate supplementation (Ref. 29). The Spina Bifida Association of America does not have a policy respecting folic acid supplementation for reduction in risk of neural tube birth defects (Ref. 30). The Teratology Society has not issued a position paper on this topic (Ref. 31).

C. Review of the Scientific Literature

1. Evidence for an Association Between Intake of Folic Acid and Neural Tube Birth Defects

a. *Criteria used in evaluating studies.* Observational studies have suggested that environmental factors such as nutritional deficiencies of vitamins may be associated with the development of neural tube defects (Ref. 32). Such observations stimulated several epidemiological studies and clinical trials. This relationship has also been investigated in some animal studies.

FDA evaluated scientific evidence available from both human and animal studies against general criteria for good experimental design, execution, and analysis. The criteria that FDA used in evaluating human epidemiologic and clinical studies included (as appropriate):

(1) Reliability and accuracy of methods used in dietary assessment;

(2) Potential for misclassification of subjects with regard to dietary intake or supplement intake;

(3) Presence of recall bias and interviewer bias;

(4) Methods of determination of vitamin status;

(5) Methods of assignment of subjects to treatment or control groups for clinical trials;

(6) Choice of control subjects and representativeness of subjects;

(7) Control of confounding factors, such as demographic variables;

(8) Assessment of compliance with treatment regimens and degree of compliance.

The criteria used in evaluating studies in animals included:

(1) Appropriateness of the animal species, diets, and treatment regimens selected for study;

(2) Whether confounding factors were controlled;

(3) Whether the number of animals was large enough to produce reliable data;

(4) Whether duration of exposure and period of observation were appropriate; and

(5) Whether methods used in the measurement of responses were reliable and accurate.

FDA placed particular emphasis on those human studies that specifically addressed the issue of folic acid and neural tube defects. Those human studies that considered effects of combinations of nutrients were given less weight because they did not address the specific question of a relationship between folic acid and neural tube defects which was identified in the 1990 amendments.

Moreover, because the ability to generalize results obtained from studies of small populations to the much larger population of women in the United States is an important consideration, FDA also evaluated human studies with respect to whether the reported results could reasonably be extrapolated to the United States population. Additionally, because health claims will be directed to the general population of healthy adults, FDA did not evaluate studies describing special situations in which use of specific medications led to the development of vitamin deficiencies because these situations require medical supervision.

FDA evaluated the weaknesses and strengths of individual human studies (see "comments" in Tables 1 through 3). It then assessed the strength of the overall evidence (e.g., epidemiologic studies, assessment of maternal vitamin status, intervention trials, animal studies) taking into account the strength of the association, the consistency of findings, specificity of the association, evidence for a biological mechanism, and presence or absence of a dose-response relationship. FDA's conclusions are based upon the strength, consistency, and preponderance of data.

b. *Human studies.* Human studies on the association between folic acid use, multivitamin use, or maternal nutrition and neural tube defects are summarized in Tables 1 through 3. The major features of these studies (type and design of study, number of women studied, location of populations, nature and duration of treatment or supplement use, maternal diet assessments, and blood indices measured and the significant results) are included in these tables.

Human studies reported to date include four supplementation trials undertaken to reduce the recurrence rate of neural tube defects (Refs. 15, 18, 19, 33, and Table 1), and three casecontrol studies (Refs. 34, 35, 36, and Table 2) and one prospective cohort study (Ref. 37 and Table 2) undertaken to identify possible associations between multivitamin use or dietary folic acid intake and incidence of neural tube defects. There have also been a number of studies in which levels of various vitamins were measured in blood samples obtained from women during or following the periconceptional interval (Refs. 14, 38, 39, 40, and Table 3).

TABLE 1.—STUDIES OF EFFECTS OF PERICONCEPTIONAL FOLATE OR MULTIVITAMIN+MINERALS SUPPLEMENTATION ON RECURRENCE OF NEURAL TUBE DEFECTS

Reference study	Type	Location	Design	NTD defined [1, 2]	Subjects	Treatment	Duration begin	End	Recurrences	Comments
Laurence et al., 1981 (Ref. 18).	Recurrence.	South Wales.	Placebo-controlled double-blind clinical trial.	Yes.....	60 treated .... 51 placebo...	4 mg folic acid per day or placebo.	Cessation of contraception.	6 weeks into gestation.	3.3 percent among supplemented 7.8 percent among placebo.	Differences were not significant. Twenty-seven percent of treated group did not comply. Protective effect reached level of significance only when apparent noncompliers were removed. All 6 women who had NTD recurrences also had inadequate diets.
Smithells et al., 1983 (Ref. 19).	Recurrence.	United Kingdom (multicenter trial).	Prospective cohort.	Yes.....	454 supplemented. 519 unsupplement- ed.	Multivitamin + calcium + iron daily (folic acid in multivitamin = 0.36 mg per day) or unsupplemented.	Not less than 28 days before conception.	Approximately 6 weeks into gestation.	0.7 percent among fully supplemented 4.7 percent among unsupplemented.	Some NTD recurrences and some other major malformations occurred in fully supplemented subjects. Questionable exclusion of 4 fully supplemented subjects, 2 of whom subsequently had NTD infants, due to difficulty with precise timing.
Vergel et al., 1990 (Ref. 33)	Recurrence.	Cuba.....	Prospective cohort.	No.....	81 treated .... 20 partially supplemented. 114 unsupplemented.	5 mg folic acid per day or unsupplement- ed.	Not less than 1 month before conception for fully supplemented.	10th week of pregnancy.	0 percent among supplemented. 0 percent among partially supplemented. 3.5 percent among unsupplemented.	Differences were not statistically significant. Unsupplemented women were seen later in pregnancy than were supplemented women. Possible bias in recruitment of subjects. Folic acid status was measured in only part of the fully supplemented group and in none of the unsupplemented group.
Wald, 1991 (Ref. 15).	Recurrence.	International multicenter trial in 7 countries.	Randomized double-blind prevention trial.	Yes.....	1,817 women were recruited of whom 1,195 subsequently had informative pregnancies.	(A) Ca+Fe +4 mg folic acid per day. (B) Ca+Fe +4 mg folic acid per day+multivitamins. (C) Ca+Fe..... (D) Ca+Fe +multivitamins.	At randomization (unspecified time before conception).	End of first trimester (12 weeks of pregnancy).	Group (A), 2/298; (B), 4/295; (C), 13/300; (D), 8/302. Recurrence rate among women in groups (A+B) was 1.0 percent. Recurrence rate among women in groups (C+D) was 3.5 percent.	Significant protective effect of folic acid on recurrence of NTDs. There was no evidence that vitamins other than folic acid conferred the protective effect. Six NTDs recurred in women in groups A+B. Lack of compliance was unlikely as an explanation for these failures. There was no excess of non-NTD birth defects reported in any one group.

[1] NTD, neural tube defect, defined as anencephaly, encephalocele, spina bifida cystica (Laurence et al., 1981; Ref. 18) and as anencephaly, encephalocele, cranial meningocele, iniencephaly, myelocele, myelomeningocele and excluding isolated hydrocephalus and spina bifida occulta (Smithells et al., 1983; Ref. 19).
[2] NTD, neural tube defect, defined as anencephaly, spina bifida cystica and encephalocele by Wald, 1991 (Ref. 15). Multivitamin preparations contained vitamins A, D, B_1, B_2, B_6, C, and nicotinamide.

TABLE 2.—STUDIES OF ASSOCIATIONS BETWEEN PERICONCEPTIONAL MULTIVITAMIN USE AND/OR DIETARY FOLATE INTAKE AND OCCURRENCE OF NEURAL TUBE DEFECTS

Reference study	Type	Location	Design	NTD defined [1 2]	Birth years	Subjects	Reported use of supplements	Other	Duration of periconceptional use	Recall interval	Results	Comments
Mills et al., 1989 (Ref. 34).	Occurrence.	CA, IL	Case-control.	Yes	1985 to 1987.	571 NTD. 546 other defects-controls. 573 normal controls.	13 to 15 percent in each group.		30 days before 1st day of last menstrual period and continuing for 45 days.	Less than 5 months.	Mothers of infants/fetuses with NTD were no less likely to have taken multivitamins or folate in periconceptional interval than were women in the control groups. Use of multivitamin supplements not associated with reduction in frequency of NTD.	Cases, controls matched for age, race, education, family income, gavidity. Attempts made to minimize recall bias. Information on multivitamin use obtained after abnormal birth was identified. Not all cases could be identified and interviewed.
Bower and Stanley, 1989 (Ref. 35).	Occurrence.	Western Australia.	Case-control.	Yes	1982 to 1984.	77 NTD. 77 other defects-controls.	15 to 21 percent in each group.	Food frequency questionnaire covering 12 month interval.	3 months before to 9 months after last menstrual period.	Not stated (possibly at least 1 year).	Increasing intake of folate (assessed by dietary intake and folate supplementation) in 1st 6 weeks of pregnancy was protective against occurrence of isolated neural tube defects.	No evidence for a protective effect of conjugated folate. Protective effect also observed for dietary fiber, calcium, vitamin C, and carotene. Measures of post-partum dietary folate status showed no association with occurrence of NTD births.
Mulinare et al., 1988 (Ref. 36).	Occurrence.	Metropolitan Atlanta.	Case-control (Atlanta Birth Defects Case-control Study).	Yes	1968 to 1980.	349 NTD. 2,829 controls.	Case mothers, 7 percent. Control mothers, 15 percent.	Maternal diet not assessed.	3 months prior to pregnancy through 1st trimester.	2 to 16 years.	Estimated risk of having NTD-affected infant was significantly lower for multivitamin users (approximately) 2.5-fold protective effect). Protective effect less pronounced when cases were compared to abnormal controls.	Compositions of multivitamin preparations not known. Users were different from nonusers in some demographic, health-related, lifestyle characteristics. Apparent protective effect was significant for whites but not for other races. Maternal nutrition during periconceptional period not known. No major differences seen for early and late postconceptional use.
Milunsky et al., 1989 (Ref. 37).	Occurrence.	New England (86 percent); other (14 percent).	Prospective cohort-women who underwent screening at about week 16 of pregnancy.	Yes	1984 to 1987.	49 NTD 22,727 controls.	31.9 percent of entire cohort used multivitamins during periconceptional interval.	Maternal diet assessed.	3 months prior to pregnancy through 1st trimester.	Several months.	Prevalence of NTD was significantly lower for women who used multivitamins with folate during periconceptional interval. Among nonusers, prevalence rates were lower for those whose diets provided >100 micrograms (μg) folate per day.	A substantial majority of the preparations contained vitamins A, C, D, and/or E. The possibility cannot be ruled out that vitamins A, C, D, and E alone or in combination(s) with folic acid were protective. Users were defined as taking at least one multivitamin per week but the majority took preparations more frequently.

[1] NTD, neural tube defect, defined as anencephaly, meningocele, encephalocele, rachischisis, iniencephaly, lipomeningocele (Mills et al., 1989; Ref. 34). Isolated hydrocephalus, hydranencephaly, dermal sinus, and spina bifida occulta were excluded from cases, and oral cleft, deformation, cosmetic defects and hydrocephalus were excluded from defect controls by Mills et al. (Ref. 34). NTDs were defined as anencephaly, spina bifida and encephalocele by Bower and Stanley (Ref. 35).

[2] NTD, neural tube defect, defined as anencephaly and spina bifida (Mulinare et al., 1988; Ref. 36) and as any combination of spina bifida, anencephaly, or encephalocele alone or in combination with other defects (Milunsky et al. 1989; Ref. 37).

TABLE 3.—MEASUREMENTS OF MATERNAL VITAMIN STATUS AS RELATED TO CENTRAL NERVOUS SYSTEM DEFECT- OR NEURAL TUBE DEFECT-PREGNANCIES

Reference	Location	Subjects and samples	Major findings
Smithells et al., 1976 (Ref. 14).	Leeds, UK	Approximately 900 women. Blood samples were obtained not more than 13 weeks after the start of the last menstrual period.	Mean values for all vitamin levels determined were most satisfactory for women in the highest social classes. Values for erythrocyte and white blood cell ascorbate were significantly lower in women who subsequently had an infant with a CNS [1] defect than in control women. Mean values for serum folate and saturation index for riboflavin were also poorer among women who had an infant with a CNS defect than mean values for all social classes.
Molloy et al., 1985 (Ref. 48).	Dublin, UK	32 NTD [2] cases, 395 controls. Blood samples obtained from 8 to 32 weeks of gestation.	Maternal serum folate and vitamin B_{12} were not significantly different between cases and controls. An hypothesized association between vitamin B_{12} deficiency and anencephaly was not confirmed in this study.
Yates et al., 1987 (Ref. 49).	Scotland, UK	20 women with history of 2 or more NTDs, 20 matched controls. Blood samples obtained after birth of index case.	Erythrocyte folate was significantly lower in women who had 2 or more NTDs than in controls. No differences in serum folate, vitamin B_{12}, or other serum vitamin measurements (plasma or white blood cell vitamin C, vitamin A, thiamine, riboflavin, pyridoxine, vitamin E) between cases and controls. Distributions of dietary folate intakes were not significantly different among groups.
Mills et al., 1991 (Ref. 50).	Finland	89 NTD cases, 172 controls. Over 85 percent of blood samples obtained within 8 weeks of neural tube closure.	No significant differences between cases and controls in serum levels of folate, vitamin B_{12}, or retinol.

[1] CNS, central nervous system. Specific abnormalities of CNS not defined by Smithells et al. (Ref. 14);
[2] NTD, neural tube defect. Cases of anencephaly, spina bifida, and encephalocele reported by Molloy et al. (Ref. 48); not defined by Yates et al. (Ref. 49) or Mills et al. (Ref. 50).

i. *Recurrence trials.* Of the four intervention trials with women who were at high risk of neural tube defect-affected pregnancies because of a history of such pregnancies (that is, women at high risk of a recurrence) (Refs. 15, 18, 19, 33, and Table 1), three trials involved daily supplementation with 4 or 5 mg of folic acid alone during the periconceptional interval (Refs. 15, 18, and 33). Two of these trials did not find a statistically significant reduction in neural tube defects. In one of these studies (Ref. 18), 27 percent of the folic acid-treated group did not comply with the treatment regimen. A statistically significant difference between treatment and control groups was found only when apparent noncompliers (identified on the basis of arbitrarily determined serum folate values) were discounted (Ref. 18).

A second intervention study involving daily supplementation with 5 mg folic acid alone was a prospective cohort

study carried out in Cuba (Ref. 33 and Table 1). Although this study showed a decreased risk of recurrence of neural tube defect-affected infants in the supplemented women, the reduction was not statistically significant. Furthermore, a bias in recruitment may have occurred because unsupplemented women in this study were seen later in pregnancy than were supplemented women. The characteristics of a "partially supplemented" group with respect to folic acid treatment were not defined (Ref. 33). Folic acid status was measured in only some women in the fully supplemented group and in none of the women in the unsupplemented group.

An intervention trial that did find a statistically significant difference in the recurrence rate of neural tube defects between supplemented and unsupplemented women (Ref. 19) measured the use of a multivitamin preparation containing folic acid, vitamins A and D, thiamine, riboflavin, pyridoxine, nicotinamide, and ascorbic acid plus minerals (ferrous sulfate and calcium phosphate) rather than folic acid alone. Daily folic acid intake from the multivitamin plus minerals preparation was 360 mg (0.36 mg). The design of this study was inadequate to test the hypothesis that folic acid supplementation would reduce the rate of recurrence of neural tube defects in women who had previously given birth to infants with neural tube defects because intakes of other nutrients in addition to folic acid were also increased in the supplemented women.

The results of a major randomized double-blind prevention trial to determine whether supplementation with folic acid alone or in combination with seven other vitamins could reduce the risk of neural tube defects in women at high risk because of a previous affected pregnancy were reported in July 1991 (Ref. 15). This international study involved women in 33 centers in the United Kingdom, Hungary, Israel, Australia, Canada, the USSR, and France. The study began in 1983 under the supervision of the Medical Research Council, United Kingdom, and was stopped in 1991, because of findings of a significant protective effect of folic acid supplementation against recurrences of neural tube defects in infants of women at high risk of this complication.

The major features of this study are included in Table 1. Women with epilepsy were excluded to avoid adverse effects of high folic acid supplementation on their treatment. A total of 1,817 women at high recurrence risk of neural tube defect pregnancies were randomized to the four treatment groups. Women remained in the trial in the same randomization groups until they had a pregnancy in which the fetus could be classified as having or not having a neural tube defect. Such outcomes were defined as "informative" pregnancies. One thousand one hundred ninety-five women of the 1,817 women randomized (66 percent) had such an informative pregnancy. Two hundred eighty-seven of these informative pregnancies (24 percent) were reported from Glasgow, Scotland, and 201 (17 percent) were reported from Budapest, Hungary, both areas of known high prevalence rates of neural tube defects.

All fetuses and infants were examined. Independent corroboration of all reported neural tube defects was obtained with a necropsy report or a description of the lesions for independent review without knowledge of the allocated group. Final results were based upon the results of all informative pregnancies. The characteristics of the 622 women who did not have informative pregnancies (34 percent of the number randomized) have not as yet been reported (Ref. 15).

Information was obtained for all abnormalities other than neural tube defects in all informative pregnancies. This information provided the basis for a determination that supplementation with folic acid specifically affected rates of recurrence of neural tube defects. The variety of other birth defects that occurred were evenly distributed across all randomization groups. The results of this carefully performed study showed that folic acid at 4 mg per day, with or without other vitamins, significantly reduced the risk of recurrences of neural tube defects in women at high risk of this complication. Six neural tube defects recurred in women in the folic acid-supplemented groups, however, showing that factors other than folic acid status are important in the etiology of neural tube birth defects. The trial had sufficient power to demonstrate efficacy of the treatment for women at high risk of recurrence but did not have sufficient power to answer questions of safety for these women.

ii. *Occurrence studies.* Two case-control studies and one prospective cohort study (Refs. 35, 36, 37, and Table 2) found associations between reduced rates of neural tube defects and use of multivitamin supplements in the periconceptional interval. In one case-control study of multivitamin use in women in the Atlanta area (Ref. 36), the compositions of multivitamin preparations used during the periconceptional interval could not be ascertained because of lengthy recall intervals. In this study, supplement use was based upon recall of events occurring 2 to 16 years before the interview (Ref. 36).

A prospective study of women in the Boston area found that use of a multivitamin supplement that contained folic acid during the first 6 weeks of pregnancy was associated with a reduction in the incidence of neural tube defects, and that no effects were observed if use of the folic acid-containing supplement began after the 6th week of pregnancy (Ref. 37). Estimation of when the use of supplements began during pregnancy depended upon self-reported pregnancy duration, which was in practice based on the date of the woman's last menstrual period (Ref. 37). The majority of the preparations reported as used in this study (Ref. 37) contained vitamins A, C, D, or E in addition to folic acid, however. Therefore, the protective agent cannot be identified. In this same study, dietary folic acid intake was calculated by means of the diet portion of the study questionnaire only for those women who were not taking a multivitamin supplement. Nonusers of multivitamin supplements who had dietary folate intakes greater then 100 μg per day had a lower incidence of neural tube defects than did nonusers whose diets provided less than 100 μg of folic acid per day (Ref. 37). Estimated intakes of nutrients other than folic acid were not reported (Ref. 37).

In a case-control study carried out in western Australia (Ref. 35 and Table 2), apparent protective effects were found for folic acid. However, this study found that dietary fiber, calcium, vitamin C, and carotene were also apparently protective against the occurrence of neural tube defects. This study found that free folate appeared to provide a stronger protective effect against occurrence of isolated neural tube defects than did total folate. Such an observation, if confirmed, may imply the existence within subgroups in the Australian population of a defect (possibly genetic) in intestinal conjugase activity (the enzyme activity that breaks down food-derived folylpolyglutamates) that would be expected to reduce the availability of food-derived folate. Alternately, such a result may represent problems in estimating folate contents of diets from food composition tables.

An additional case-control study involving women in California and Illinois did not find a protective effect on the incidence of neural tube defects from the use of folate-containing multivitamin preparations during the

periconceptional interval (Ref. 34 and Table 2). Supplement usage among women who had a neural tube defect-complicated pregnancy was compared to usage of supplements among women who had normal infants as well as to supplement usage among women who had infants born with abnormalities other than neural tube defects. Use of multivitamin supplements was reported to be the same among women in all three groups, and no protective effect was identified (Ref. 34).

Commentaries on the four studies cited above have been numerous (Refs. 38–46) and include considerations of the role of health-conscious behavior in reduction in risk of neural tube defects (Ref. 38), significance of biases in recall (Ref. 39), problems with case-identification methods (Ref. 40), and differences in prevalence rates in the study areas (Ref. 44). Researchers in the United Kingdom observed, in studies with women at high risk for neural tube defect recurrences, that effects of vitamin therapy are more marked in high-prevalence areas than in low-prevalence areas (Ref. 47). It is important to note that among the four epidemiologic studies cited above, the three studies that showed a positive effect of folic acid or multivitamin supplementation involved populations of higher prevalence of neural tube defects (Boston, 3.5 neural tube defects per 1,000 births (Ref. 37); Atlanta, 1.8 per 1,000 (Ref. 36); and Perth, Australia, 1.5 per 1,000 (Ref. 35)) than did the single study that did not reveal such an effect (California and Illinois, 0.91 neural tube defects per 1,000 births (Ref. 34)). The prevalence factor may be highly important when a multifactorial condition is under investigation, and when prevention or reduction in risk is attempted through manipulation of the environmental (for example, nutritional) component (Ref. 41). The environmental contribution to the total etiology is thought to be greater in areas of higher prevalence. Consequently, in low prevalence areas, a higher percent is attributable to genetic factors and less is attributable to environmental factors (Ref. 41).

None of the epidemiologic studies was able to identify any one factor that was specifically related to reduction in risk of neural tube defects. Maternal dietary counseling and maternal dietary improvement appeared to be as effective a measure as supplementation in decreasing the risk of having an infant affected with a neural tube defect (Ref. 60). Furthermore, all of these epidemiologic studies suffered from biases, including problems with differences in length of recall (Ref. 36), differences between cases and controls relative to socioeconomic status and lifestyle characteristics (Ref. 36), nonrepresentativeness of subjects (Ref. 37), inability to identify and interview all cases (Ref. 34), and possible inaccuracies in determining dietary folate content from food composition tables (Ref. 35). In summary, the results of these occurrence studies do not provide a basis on which to find an association between ingestion of folic acid and reduction in risk for neural tube defects.

iii. *Measurements of maternal vitamin status.* Clinical measures of maternal vitamin status (including folate) also provide no evidence for a consistent association between folic acid intake and neural tube defects. One study (Ref. 14, Table 3) showed that mean blood values for all vitamins determined were most satisfactory for women in the highest social classes. Additionally, mean values for several vitamins were poorer among women who had an infant with a CNS defect than mean values for all social classes (Ref. 14).

Another study (Ref. 49 and Table 3) reported that erythrocyte folate values were significantly lower among women who had repeated neural tube defect pregnancies than among controls. However, dietary intakes of folate among the groups of neural tube defect-affected mothers and control mothers were not significantly different and did not correlate with pregnancy outcome. Thus, an association between risk of having offspring with neural tube defects and decreased erythrocyte folate levels could not be attributed to lower dietary folate intake by the mothers of neural tube defect-affected infants (Ref. 49). Another study did not find differences in parameters of folate status between mothers of neural tube defect infants and controls (Ref. 48).

A report of maternal serum vitamin measurements in a population-based study of Finnish women who gave birth to infants with neural tube defects (Ref. 50 and Table 3) found no significant difference in serum folate levels between women who gave birth to a neural tube defect-affected infant and control women (Ref. 50).

c. *Animal studies.* Studies with animal model systems are one of several lines of investigation that are used to establish associations between deficiencies or excesses of various nutrients and birth defects. Such studies have provided some support for the hypothesis that nutrient deficiencies may be one factor in the etiology of neural tube defects (Ref. 51).

Deficiencies of nutrients such as vitamin B_{12}, vitamin B_6, pantothenic acid, and vitamin E have been reported to cause neural tube defects in some species (Ref. 1).

In rats, maternal folic acid deficiency alone does not produce neural tube defect-affected embryos in a reproducible manner (Ref. 26). However, rats fed folate-deficient diets in conjunction with antifolates during pregnancy do produce embryos with multiple congenital abnormalities (Ref. 52). A high spontaneous rate of neural tube defects that closely resemble those seen in humans occurs in the curly-tail mouse. These defects appear to be related to a recessive gene whose expression is modified by the rest of the genome (the complete set of hereditary factors contained in the chromosomes) (Ref. 53). Excess vitamin A administered on the 8th day of gestation increased the incidence of neural tube defects in this mouse in a dose-dependent manner. A variety of compounds including folic acid, folinic acid, methotrexate, vitamin B_{12}, and vitamin E did not significantly affect the incidence of the defect in this model system (Ref. 54).

Neural tube defects in the golden hamster model can be induced by maternal hyperthermia or ethanol following exposures early in gestation. Folate supplementation begun before such treatments does not prevent the alcohol or heat-induced neural tube defects (Ref. 55).

Neural tube defects can be induced by administration of the anticonvulsant drug valproic acid to mice on the 8th day of gestation (Ref. 56). The administration of 5-formyltetrahydrofolate, an active metabolite of folic acid, significantly reduces the rates of these defects. The authors of this study suggested that this model system may be appropriate for studies of protective effects of folates on occurrence of neural tube defects (Ref. 56). Results of mechanistic studies directed toward identifying valproic acid-induced disturbances in folate metabolism have been reported (Ref. 57).

The results of animal studies do not provide evidence for a consistent association between folic acid nutriture and neural tube defects but show that disturbed folate metabolism may be one factor in the complex etiology of neural tube defects.

2. Other Relevant Information

a. *Evidence for efficacy of Periconceptional supplementation of women at high risk of neural tube defect pregnancies with less than 4 mg folic acid per day.* The daily intake of folic

acid that significantly reduced the risk of recurrences of neural tube defects in high-risk women in the United Kingdom trial was 4 mg and was provided as a supplement (Ref. 15). A daily folic acid intake of 4 mg cannot be attained from usual diets, even when such diets are high in folate-rich foods such as dark green leafy vegetables and liver. Additionally, food additive regulations in the United States do not permit addition of folic acid at high levels to foods or supplements (21 CFR 172.345). Therefore, the agency examined the results of all available human studies to determine whether such studies provide data showing that significant reductions in risk of neural tube defects occurred with intakes of folic acid below 4 mg per day and within the range of folic acid intake attainable in usual diets.

The agency examined the results of both intervention and epidemiologic studies. Only one of four human intervention trials involved supplementation with less than 4 or 5 mg folic acid per day (Ref. 19). A nonrandomized intervention trial carried out in the United Kingdom found a significant difference in the recurrence rate of neural tube defects between women given a multivitamin plus minerals supplement and those who were not supplemented. The multivitamin plus minerals supplement given to some of the women provided folic acid at 360 μg per day. No true control group was included in this trial. Supplemented women were recruited well before conception while unsupplemented women were already pregnant before referral to the study. The design of this study was inadequate to test the hypothesis that folic acid supplementation would reduce the risk of recurrence of neural tube defects in women who had previously given birth to infants with such defects because the supplement used contained a number of vitamins and two minerals in addition to folic acid.

In this study (Ref. 19), attempts were made to examine all infants of fully-supplemented mothers to determine whether vitamin supplementation might harm the embryo or fetus. Results of such examinations were reported for only part of the fully-supplemented group but not for partially-supplemented or unsupplemented groups (Ref. 19). Thus, no comparison of effects between supplemented and unsupplemented groups was possible. The proportions of spontaneous abortions examined in fully-supplemented and unsupplemented women were 61 percent in the first cohort and 32 percent in the second cohort reported (Ref. 19). In contrast, results of all informative pregnancies were reported in the recently published Medical Research Council trial (Ref. 15), leading to virtually complete ascertainment of treatment effects. Thus, efficacy of a dose of folic acid of 360 μg cannot be determined from Ref. 19.

Examination of epidemiologic studies for information pertaining to efficacy of lower doses of folic acid did not provide definitive results. For example, in one study that reported that use of multivitamins containing folic acid reduced the risk of having a neural tube defect-affected infant, the compositions of the multivitamin preparations containing folic acid were not known because of long recall intervals (2 to 16 years) (Ref. 36). In another study that reported that the prevalence of neural tube defects was significantly lower for women who used multivitamins during the periconceptional interval than for women who did not, the multivitamin preparations contained folic acid at levels of 100 to 1,000 μg (Ref. 37). A substantial majority of the preparations also contained vitamins A, C, D, or E. In this study, an efficacious dose of folic acid could not be identified and the possibility could not be ruled out that other vitamins alone or in combination with folic acid were protective.

These studies (Refs. 19, 36, and 37) do not provide sufficient evidence that doses of folic acid lower than 4 mg per day provide significant reductions in risk of recurrence of neural tube defect-affected pregnancies. Thus, evidence of efficacy of doses of folic acid lower than 4 mg per day is lacking. The agency tentatively concludes, based on the currently available evidence, that the amount of folic acid supplementation needed for reduction in risk of neural tube defects in women at high risk of this complication is the level used in the Medical Research Council vitamin study (i.e., 4 mg per day) (Ref. 15).

b. *Significance of studies with anticonvulsant drugs.* FDA recognizes that there is a considerable literature on possible roles of drug-induced nutritional deficiencies in causation of birth defects. Anticonvulsant drugs taken during pregnancy are among a number of factors implicated in the increased risk of congenital malformations including neural tube defects reported in children of women with epilepsy. Abnormalities in vitamin status for biotin, folate, 25-hydroxy-vitamin D, and vitamin A have been reported in anticonvulsant-treated epileptic women. FDA believes that serious medical conditions such as epilepsy should be handled under medical supervision, and that nutritional guidance for anticonvulsant-treated pregnant women or anticonvulsant-treated women planning pregnancy should be provided by trained medical personnel.

c. *Safety considerations.* In "Nutrition During Pregnancy," NAS reviewed the safety of folic acid intake during pregnancy (Ref. 3). It found that the safety of large doses of folic acid during pregnancy had not been systematically evaluated, and that the effects of large maternal doses of folate on the developing fetus are not known (Ref. 3). NAS cited studies (Refs. 58 and 59) that suggested that large doses of folic acid may inhibit the absorption of other nutrients by competitive interaction. Large doses of folic acid may also make it more difficult to diagnose the onset of, or a relapse of, pernicious anemia (Ref. 3). This fact is important because pernicious anemia may occur in pregnant women with impaired vitamin B_{12} absorption caused by lack of intrinsic factor, gastrectomy, or small intestinal disorders that affect the ileum.

The National Research Council, in its 1989 edition of the "Recommended Dietary Allowances" (Ref. 24), also reviewed effects of excessive intakes and toxicity of folic acid in humans and animals. The National Research Council (Ref. 24) concluded that without evidence of benefit, and with some potential for toxicity, excessive intakes of supplemental folic acid are not recommended.

The Medical Research Council vitamin study (Ref. 15) examined effects of supplementation with 4 mg folic acid per day in fetuses and mothers. The number of reported congenital abnormalities other than neural tube defects was similar in all four groups. The mean number of women reporting various medical disorders during the study was also similar in all groups. Thus, supplementation of women at high risk of neural tube defect pregnancies with 4 mg folic acid per day during the periconceptional interval was not associated with adverse effects, but the ability of the study to identify such effects was limited by the size of the groups.

The design of the United Kingdom trial was sufficient to demonstrate efficacy of folic acid supplementation in high-risk women (Ref. 15). It did not however, have sufficient power to evaluate safety for these high-risk women or for broader public health purposes. The study did not examine the benefit or risk of folate supplementation among low-risk women (those who are not at risk of recurrence of a neural tu-

defect-affected pregnancy). Unanswered questions of major concern include those of efficacy and safety of similar intervention in the much larger population of women in the United States at considerably lower risk of occurrence of neural tube defect-complicated pregnancies. There are currently no data demonstrating safety of long-term supplementation of women of child-bearing age with folic acid at the dose used in the United Kingdom Medical Research Council vitamin trial.

3. Conclusions

Until the July 1991 publication of the Medical Research Council's report (Ref. 15), the human studies on the hypothesized association between ingestion of folic acid and reduction in risk of neural tube defects were limited in design and were inconsistent in their findings. Human intervention trials using folic acid would be expected to provide the strongest evidence for efficacy of folic acid supplementation if such trials demonstrated significant reductions in the risk of neural tube defects following folic acid supplementation. Two early trials examining periconceptional supplementation with 4 or 5 mg folic acid alone in women at high risk of neural tube defect recurrences produced nonsignificant results (Refs. 18 and 33). A single nonrandomized intervention study that did find a statistically significant reduction in neural tube defects in women at high recurrence risk of this complication measured usage of a multivitamin plus minerals supplement in addition to folic acid rather than folic acid alone (Ref. 19) and thus, could not demonstrate an independent effect of folic acid supplementation.

The Medical Research Council's randomized double-blind multi-center trial (Ref. 15) clearly demonstrated a significant reduction in recurrence rate of neural tube defects in women supplemented kingdom with 4 mg folic acid per day. No protective effects of vitamins other than folic acid were observed (Ref. 15), and no data were provided to demonstrate the efficacy of doses lower than 4 mg per day. This study established a specific role for folic acid in reduction in risk of recurrence for a significant proportion of neural tube birth defects in women at high risk for this complication because of a history of neural tube defect pregnancies and has provided useful information on an important medical question (Ref. 59).

The four human intervention trials reported to date have been recurrence trials carried out in women in the United Kingdom, Hungary, Israel, Australia, Canada, the USSR, France, and Cuba in women with known high risks of neural tube defect-complicated pregnancies (Refs. 15, 18, 19, and 33). The high incidence of neural tube defects among women in Scotland and in Ireland has made these areas a focus of interest for studies of neural tube defects for many years. Studies in such high incidence areas as those mentioned above enhance the ability to examine cause and effect relationships.

Determination of whether the findings of the Medical Research Council trial with respect to supplementation of women at high risk of recurrent neural tube defect-complicated pregnancies can be extrapolated to other populations at much lower risk is problematic. As noted above, the Medical Research Council trial demonstrated efficacy of folic acid supplementation only in women at known high risk of recurrence of neural tube defect-complicated pregnancies because of a prior history of such a pregnancy. It did not examine effects of such supplementation in women at much lower risk of a first occurrence of a neural tube defect. It is important to note that the recurrence rate of neural tube defects in folate-supplemented women in the Medical Research Council trial was 1 percent (Ref. 15). This rate is at least 10 times higher than the rate of occurrence of neural tube birth defects in the general United States population and emphasizes the important distinction that must be made between risk of occurrence and risk of recurrence of neural tube defects.

The ability to project efficacy of folic acid intervention under U.S. dietary and lifestyle conditions is limited by the fact that none of the four intervention trials were carried out in the United States, an area of very low risk relative to the other areas studied. Moreover, the results of these intervention studies, which examined only recurrences of neural tube defects in areas of high prevalence, may not be generalizable to the considerably larger population of women in the United States who are at a much lower risk for a first occurrence of a neural tube defect-affected pregnancy.

The ability to generalize results obtained from studies of high-risk populations to the much larger population of "all women of child-bearing age" who would be targeted by specific health claims is an important concern. There is a question as to whether data obtained from recurrence trials abroad (Refs. 15, 18, 19, and 33) can be extrapolated to women in the United States who have never had a neural tube defect pregnancy.

Considerations of the ability to generalize results also pertain to several epidemiologic studies carried out in the United States. For example, the authors of a large prospective cohort study of the occurrence of neural tube defects recruited women who were receiving prenatal care and had a maternal alphafetoprotein screen or an amniocentesis (Ref. 37). Such women are not representative of pregnant women in the general population. The results of another study found that the apparent protective effects of periconceptional multivitamin use were statistically significant for white women but not for women of other races (Ref. 36). Racial differences in risks for neural tube defects are well-recognized (Ref. 2).

In general, women included in these studies on neural tube defects may not be representative of an entire population of women at lower risk because those who take or are willing to take supplements may have other characteristics that by themselves decrease the risk of having an infant with a neural tube defect. For example, women who have had a neural tube defect-complicated pregnancy and who are seeking to avoid a recurrence may be more willing to seek medical advice before conception, or to take a supplement during the periconceptional interval, than women who have never had a birth defect-affected pregnancy. The fact that the sizes of the populations studied and their risks for neural tube defect pregnancies differed widely further complicates a determination as to whether such results can be generalized to a potential target population including all women in the United States of child-bearing age.

To date, a relationship between inadequate dietary intake of folic acid and increased risk of neural tube defects has not been established. The Medical Research Council's multi-center trial did establish that periconceptional supplementation of women at high risk of neural tube defect pregnancies with 4 mg folic acid per day led to significant reductions in recurrences of neural tube defects (Ref. 15). The trial did not, however, demonstrate a total elimination of recurrent neural tube defect complications in the high-risk women. In the Medical Research Council's study, 6 of 27 reported neural tube defects (22 percent) recurred in women in groups receiving folic acid supplementation. Since serum folate levels in these women were not unusually low for supplemented women, lack of compliance with the supplementation or failure to absorb folic acid were unlikely explanations for

these recurrences (Ref. 15). Thus, a significant fraction of neural tube defect recurrences were apparently resistant to folic acid supplementation. The genetic or metabolic factors underlying these defects are not understood. Such observations emphasize the heterogeneous (or multifactorial) etiology of neural tube defects.

The daily intake of folic acid that significantly reduced the risk of recurrences of neural tube defects in high-risk women in the United Kingdom trial was 4 mg and was provided as a supplement (Ref. 15). As stated above, daily folic acid intake of 4 mg cannot be attained from usual diets, even when such diets are high in folate-rich foods such as dark green leafy vegetables and liver. Additionally, the amount of folic acid needed for efficacy in reducing the rates of recurrent neural tube defects in women at high risk exceeds the amount that can safely be added to foods under current food additive regulations (21 CFR 172.345). Therefore, the agency examined the results of all available human studies to determine whether such studies provide data showing that significant reductions in risk of recurrent neural tube defects occurred with intakes of folic acid below 4 mg per day and within the range of folic acid intake attainable in usual diets.

Only one of four human intervention trials involved supplementation with less than 4 or 5 mg folic acid per day (Ref. 19). This nonrandomized intervention trial measured use of a multivitamin plus minerals supplement which provided folic acid at 360 μg per day. No true control group was included in this trial. Thus, the design of the study was inadequate to test the hypothesis that folic acid supplementation would reduce the risk of recurrence of neural tube defects in women who had previously given birth to infants with neural tube defects because nutrients other than folic acid were included in the supplements (Ref. 19). Moreover, examination of epidemiologic studies for information pertaining to efficacy of doses of folic acid lower than 4 mg per day did not provide definitive results because the compositions of multivitamin preparations used could not be determined (Ref. 36) or because folic acid content of preparations varied over a wide range (Ref. 37).

Thus, because scientific evidence of efficacy of doses of folic acid less than 4 mg per day in reducing rates of neural tube defect recurrences is lacking, the agency tentatively concludes that the amount of folic acid supplementation needed for reduction in risk of recurrer neural tube defects in women at high risk of such recurrences is 4 mg per day (i.e., that level which produced significant findings in the United Kingdom trial (Ref. 15)).

The agency also considered whether claims relating intake of multivitamins including folic acid to reduction in risk of neural tube defects would meet the standard set forth in the 1990 amendments. The agency did not broaden the scope of its considerations to include, for example, multivitamins containing folic acid and other combinations of nutrients and folic acid, because the 1990 amendments clearly identified folic acid and neural tube defects as one of 10 specific topic areas for which the validity of health claims was to be determined. Furthermore, the studies that found an association between use of multivitamin supplements and reduction in risk of neural tube defects did not specify the composition of such supplements (i.e., neither the identity of the vitamins present nor their concentrations were known). Most importantly, the United Kingdom Medical Research Council trial (Ref. 15) demonstrated that vitamins other than folic acid provided no protective effect against recurrence risk of neural tube defect pregnancies (Ref. 15).

III. Tentative Decision to Deny a Health Claim Relating Ingestion of Folic Acid to Reduced Risk of Neural Tube Birth Defects

FDA is proposing not to authorize the use on the labels and labeling of foods, including dietary supplements, of health claims relating to the association between ingestion of folic acid and reduction in risk of neural tube birth defects. Health claims on foods are intended to provide consumers in the general population with information relative to relationships between usual intakes of nutrients and reductions in risk of specific diseases (see companion document "Food Labeling: General Requirements for Health Claims for Food: Proposed Rule," published elsewhere in this issue of the **Federal Register**). The amount of folic acid needed for reduction in risk of neural tube birth defects in women at high risk of this condition is significantly in excess of usual intakes and exceeds amounts permitted under current food additive regulations. FDA has determined that products that provide the necessary amount of folic acid are drugs. In addition, there is no scientific evidence that periconceptional supplementation of women of childbearing age with doses of folic acid lower than 4 mg per day will significantly reduce the risk of neural tube birth defects. For all these reasons, FDA has tentatively determined that claims on foods, including dietary supplements, relating to folic acid and reduction in risk of neural tube birth defects are not justified.

The agency recognizes the significance of the recently published Medical Research Council Vitamin trial and the importance of its findings for women at high risk of recurrence of neural tube defect-affected pregnancies. The results of this carefully performed trial demonstrated that significant reductions in risk of recurrent neural tube defects could be achieved by supplementation of women at high risk with supraphysiologic levels of folic acid. Such therapeutic use of folic acid as a drug, however, permits a risk-benefit consideration that is inappropriate for a food. Recent statements by the CDC provide guidelines for use of folic acid by those women who are planning a pregnancy and who are at high risk of such a complication (Ref. 16). Because of the importance of this guidance, FDA is reprinting significant portions of the CDC recommendations:

1. Women who have had a pregnancy resulting in an infant or fetus with a neural tube defect should be counseled about the increased risk in subsequent pregnancies and should be advised that folic acid supplementation may substantially reduce the risk for neural tube defects in subsequent pregnancies.

2. Women who have had a pregnancy resulting in an infant or fetus with a neural tube defect should be advised to consult their physician as soon as they plan a pregnancy. Unless contraindicated, they should be advised to take 4 mg per day of folic acid starting at the time they plan to become pregnant. Women should take the supplement from at least 4 weeks before conception through the first 3 months of pregnancy.

3. The 4 mg daily dose should be taken only under a physician's supervision. Tablets containing 1 mg folic acid are available as a prescription item. The folic acid dose should be obtained from pills containing only folic acid. Multivitamin (over-the-counter and prescription) preparations containing folic acid should not be used to attain the 4 mg dose because harmful levels of vitamins A and D could also be taken. Prescribing physicians should be aware of the potential for high doses of folic acid to complicate the diagnosis of vitamin B_{12} deficiency. Anemia resulting from vitamin B_{12} deficiency may be prevented with high doses of folic acid; however, the neurologic damage that can result from vitamin B_{12} deficiency could continue.

4. These recommendations are provided only for women who previously have given birth to an infant or had a fetus with a neural tube defect; they are not intended for (1) women who have never given birth to ar infant or had a fetus with a neural tube

defect, (2) relatives of women who have had an infant or fetus with a neural tube defect, (3) women who themselves have spina bifida or (4) women who take the anticonvulsant valproic acid—a known cause of spina bifida (Ref. 16).

The standard proposed in "Food Labeling: General Requirements for Health Claims for Food: Proposed Rule" (published elsewhere in this issue of the **Federal Register**) requires that a health claim be supported by the publicly available scientific evidence, and that there be significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, regarding such support. Clearly, on the issue of use of folic acid supplementation to reduce the risk of neural tube defects, there is no such evidence at levels of folic acid that can be safely added to foods (including dietary supplements), and thus there is no basis for agreement as to the appropriateness of using folic acid-containing dietary supplements to attempt to reduce the risk of neural tube defects among women in the general United States population. Thus, the agency is proposing not to authorize the use on foods and supplements of health claims relating to associations between ingestion of folic acid and reduction in risk of neural tube birth defects.

IV. Environmental Impact

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

V. Economic Impact

The food labeling reform initiative, taken as a whole, will have associated costs in excess of the $100 million threshold that defines a major rule. Therefore, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA has developed one comprehensive regulatory impact analysis (RIA) that presents the costs and benefits of all of the food labeling provisions taken together. The RIA is published elsewhere in this issue of the **Federal Register**. The agency requests comments on the RIA.

VI. Comments

Interested persons may, on or before January 27, 1992, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

VII. 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. Scott, J. M., P. N. Kirke, and D. G. Weir, "The Role of Nutrition in Neural Tube Defects," *Annual Review of Nutrition*, 10:277–295, 1990.

2. Elwood, J. M., and J. H. Elwood, "Epidemiology of Anencephalus and Spina Bifida," Oxford, Oxford University Press, 1980.

2a. Lian, Z., H-Y. Yang, and Z. Li, "Neural Tube Defect in Beijing-Tianjin Area of China," *Journal of Epidemiology and Community Health*, 41:259, 1987.

3. Institute of Medicine, NAS, "Nutrition During Pregnancy," Washington, DC, National Academy Press, 1990.

4. Steegers-Theunissen, R. P. M., G. H. J. Boers, F. J. M. Trijbels, and T. K. A. B. Eskes, "Neural-tube Defects and Derangement of Homocysteine Metabolism," *New England to Journal of Medicine*, 324(3):199–200, 1991.

5. Edwards, R. P., and R. P. Balfour, "The Clinical Diagnosis of Major Congenital Abnormalities of the Fetal Central Nervous System," *British Journal of Obstetrics and The Gynaecology*, 83:422–424, 1976.

6. Edmonds, L. D., and L. M. James, "Temporal Trends in the Prevalence of Congenital Malformations at Birth Based on the Birth Defects Monitoring Program, United States, 1979–1987," *Morbidity and Mortality Weekly Report*, 39/No. SS–4:19–23, 1990.

7. Rhoads, G. G., and J. L. Mills, "Can Vitamin Supplements Prevent Neural Tube Defects? Current Evidence and Ongoing Investigations," *Clinical Obstetrics Gynecology*, 29:569–579, 1986.

8. Slattery, M. L., and D.T. Janerich, "The Epidemiology of Neural Tube Defects: A Review of Dietary Intake and Related Factors as Etiologic Agents," *American Journal of Epidemiology*, 133:526–540, 1991.

9. Leck, I., "Teratogenic Risks of Disease and Therapy," *Enidemiologic Methods for Detection of Teratogens*, M. A. Klingbert, and J. A. C. Weatherell, eds., 1:23–43, Karger, Basel, 1979.

10. Robert, E., and F. Rosa, "Valproate and Birth Defects," *Lancet* ii:1142, 1983.

11. Lindhout, D., and H. Meinardi, "Spina Bifida and In Utero Exposure to Valproate," *Lancet* ii:396, 1984.

12. Lammer, E. J., and L. E. Sever, C. P. Oakley, Jr., "Teratogen Update: Valproic Acid," *Teratology*, 35:465–473.

13. "Valproate, Spina Bifida, and Birth Defects Registries," *Lancet* ii:1404–1405, 1988.

14. Smithells, R. W., S. Sheppard, and C. J. Schorah, "Vitamin Deficiencies and Neural Tube Defects," *Archives of Disease in Childhood*, 51:944–950, 1976.

15. Wald, N., "Prevention of Neural Tube Defects: Results of the Medical Research Council Vitamin Study," *Lancet*, 338:131–137, 1991; and editorial, "Folic Acid and Neural Tube Defects," *Lancet*, 338:153154, 1991.

16. CDC, "Use of Folic Acid for Prevention of Spina Bifida and Other Neural Tube Defects, 1983–1991," *Morbidity and Mortality Weekly Report*, 40 (30) 513–516, August 2, 1991.

17. Minister of National Health and Welfare, Canada, *Nutrition Recommendations: The Report of the Scientific Review Committee—1990*, Canadian Government Publishing Centre, Ottawa, Canada.

18. Laurence, K. M., N. James, M. H. Miller, G. B. Tennant, and H. Campbell, "Double-blind Randomized Controlled Trial of Folate Treatment Before Conception to Prevent Recurrence of Neural-tube Defects," *British Medical Journal*, 282:1509–1511, 1981.

19. Smithells, R. W., M. J. Seller, R. Harris, D. W. Fielding, C. J. Schorah, N. C. Nevin, S. Sheppard, A. P. Read, S. Walker, and J. Wild, "Further Experience of Vitamin Supplementation for Prevention of Neural Tube Defect Recurrences," *Lancet* i:1027–1031, 1983.

20. Elwood, J. M., "Can Vitamins Prevent Neural Tube Defects?", *Canadian Medical Association Journal*, 129:1088–1092, 1983.

21. U.S. Department of Health and Human Services, Public Health Service, "The Surgeon General's Report on Nutrition and Health," Washington, DC, DHHS (PHS) Publication No. 017–001–00465–1, U.S. Government Printing Office, 1988.

22. U.S. Department of Agriculture and U.S. Department of Health and Human Services, "Nutrition and Your Health: Dietary Guidelines for Americans," Home and Garden Bulletin, No. 232, 3rd ed., U.S. Government Printing Office, 1990.

23. Committee on Diet and Health, Commission on Life Sciences, National Research Council, "Diet and Health: Implications for Reducing Chronic Disease Risk," Washington, DC, National Academy Press, 1989.

24. Food and Nutrition Board, Commission on Life Sciences, National Research Council, "Recommended Dietary Allowances," 10th ed., National Academy Press, Washington, DC, 1989.

25. LSRO, "Folic Acid and Neural Tube Defects," Federation of American Societies for Experimental Biology, Bethesda, MD (under contract to FDA, 1991).

26. Dobbing, J., editor, *Prevention of Spina Bifida and Neural Tube Defects*, London, Academic Press, 1983.

27. CDC, "Periconceptional Use of Multivitamins and the Occurrence of Anencephaly and Spina Bifida," *Morbidity and Mortality Weekly Report*, 37:727–730, December 2, 1988.

28. Mills, James L., National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, memo to file, April 4, 1991.

29. Pearse, Warren, American College of Obstetricians and Gynecologists, 409 12th St.,

SW., Washington, DC, and Harold A. Kaminetzky, MD, FACOG, Director of Practice Activities, memo to file, April 4, 1991.

30. Spina Bifida Association of America, 1700 Rockville Pike, Rockville, MD, memo to file, June 27, 1991.

31. Scott, William, Chairman, Public Affairs Committee, Teratology Society, 9650 Rockville Pike, Bethesda, MD, memo to file, April 7, 1991.

32. Wald, N. J., "Neural Tube Defects and Vitamins: The Need for a Randomized Clinical Trial," *British Journal of Obstetrics and Gynecology*, 91:516–523, 1984.

33. Vergel, R. G., L. R. Sanchez, B. L. Heredero, P. L. Rodriquez, and A. J. Martinez, "Primary Prevention of Neural Tube Defects with Folic Acid Supplementation: Cuban Experience," *Prenatal Diagnosis*, 10:149–152, 1990.

34. Mills, J. L., G. G. Rhoads, J. L. Simpson, G. C. Cunningham, M. R. Conley, M. R. Lassman, M. E. Walden, R. Depp, and H. J. Hoffman, "The Absence of a Relation Between the Periconceptional Use of Vitamins and Neural-tube Defects," *New England Journal of Medicine*, 321:430–435, 1989.

35. Bower, C., and F. J. Stanley, "Dietary Folate as a Risk Factor for Neural-tube Defects: Evidence from a Case-control Study in Western Australia," *Medical Journal of Australia*, 150:613–619, 1989.

36. Mulinare, J., J. F. Cordero, J. D. Erickson, and R. J. Berry, "Periconceptional Use of Multivitamins and the Occurrence of Neural Tube Defects," *Journal of the American Medical Association*, 260:3141–3145, 1988.

37. Milunsky, A., H. Jick, S. S. Jick, C. L. Bruell, D. S. MacLaughlin, K. J. Rothman, and W. Willett, "Multivitamin/Folic Acid Supplementation in Early Pregnancy Reduces the Prevalence of Neural Tube Defects," *Journal of the American Medical Association*, 262:2847–2852, 1989.

38. Mills, J. L., G. G. Rhoads, J. L. Simpson, and G. C. Cunningham, letter to the editor, *Journal of the American Medical Association*, 263:2747–2748, 1990.

39. Shapiro, S., A. A. Mitchell, M. M. Werler, letter to the editor, *Journal of the American Medical Association*, 263:2748, 1990.

40. Milunsky, A., H. Jick, S. S. Jick, K. J. Rothman, W. Willett, "In Reply," *Journal of the American Medical Association*, 263:2748–2749.

41. Seller, M. J., and N. C. Nevin, letter to the editor, *Journal of the American Medical Association*, 263:2749, 1990.

42. Halstead, C. H., "Periconceptional Use of Multivitamins and the Prevalence of Neural Tube Defects," letter to the editor, *New England Journal of Medicine*, 322:1082, 1990.

43. Milunsky, A., H. Jick, S. S. Jick, and W. Willett, letter to the editor, *New England Journal of Medicine*, 322:1082–1083, 1990.

44. Mulinare, J., J. F. Cordero, J. D. Erickson, and R. J. Berry, letter to the editor, *New England Journal of Medicine*, 322:1063, 1990.

45. Mills, J. L., G. G. Rhoads, H. T. Hoffman, J. L. Simpson, G. C. Cunningham, and M. R. Lassman, letter to the editor, *New England Journal of Medicine*, 322:1083–1084, 1990.

46. Mulinare, J., J. F. Cordero, J. D. Erickson, and R. J. Berry, letter to the editor, *New England Journal of Medicine*, 322:1085, 1990.

47. Seller M. J., and N. C. Nevin, "Periconceptional Vitamin Supplementation and the Prevention of Neural Tube Defects in Southeast England and Northern Ireland," *Journal of Medical Genetics*, 21:325–330, 1984.

48. Molloy, A. M., P. Kirke, I. Hillary, D. G. Weir, and J. M. Scott, "Maternal Serum Folate and Vitamin B_{12} Concentrations in Pregnancies Associated With Neural Tube Defects," *Archives of Disease in Childhood*, 60:660–665, 1985.

49. Yates, J. R. W., M. A. Ferguson-Smith, A. Shenkin, R. Guzman-Rodriguez, M. White, and B. J. Clark, "Is Disordered Folate Metabolism the Basis for the Genetic Predisposition to Neural Tube Defects?", *Clinical Genetics*, 31:279–287, 1987.

50. Mills, J. L., J. Tuomilehto, K. F. Yu, W. Rundle, W. Blaner, P. Koskella, N. Colman, M. Forman, L. Toivanen, and G. G. Rhoads, "Maternal Vitamin Levels During Pregnancies Producing Infants with Neural tube defects," *Pediatric Research*, 29 (No. 4, Part 2:71A), 1991.

51. Kalter H., and J. Warkeny, "Experimental Production of Congenital Malformations in Mammals by Metabolic Procedure," *Physiological Reviews*, 39:69–115, 1959.

52. Nelson, M. M., H. V. Wright, C. W. Asling, H. M. Evans, "Multiple Congenital Abnormalities Resulting from Transitory Deficiency of Pteroylglutamic Acid During Gestation in the Rat," *Journal of Nutrition*, 56:349–369, 1955.

53. Embury, S., M. J. Seller, M. Adinolfi, and P. E. Polani, "Neural Tube Defects in Curly-tail Mice. I. Incidence and Expression," *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 206:85–94, 1979.

54. Seller, M. J., and M. Adinolfi, "The Curly-tail Mouse: An Experimental Model For Human Neural Tube Defects," *Life Sciences*, 29:1607–1615, 1981.

55. Graham J. M., and V. H. Ferm, "Heat- and Alcohol-induced Neural Tube Defects: Interactions with Folate in a Colden Hamster Model," *Pediatric Research*, 19 (2) 247–251, 1985.

56. Trotz, M., C. Wegner, and H. Nau, "Valproic Acid-induced Neural Tube Defects: Reduction by Folinic Acid in the Mouse," *Life Sciences*, 41:103–110, 1987.

57. Wegner, C. H. R. and N. Nau, "Valproic Acid-induced Neural Tube Defects: Disturbance of the Folate Metabolism in Day 9 Mouse Embryo," *Teratology*, 39:488, 1989.

58. Ghishan, F. K., H. M. Said, R. C. Wilson, J. E. Murrell, and H. L. Greene, "Intestinal Transport of Zinc and Folic Acid: A Mutual Inhibitory Effect," *American Journal of Clinical Nutrition*, 43:258–262, 1986.

59. Simmer, K., C. James, and R. P. H. Thompson, "Are Iron-folate Supplements Harmful?", *American Journal of Clinical Nutrition*, 45:122–125, 1987.

60. Laurence K. M., "Dietary Approaches to the Prevention of Neural Tube Defects," *Nutrition and Health*, 2:181–189, 1983.

List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

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

PART 101—FOOD LABELING

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

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355 371).

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

§ 101.71 Health claims: claims not authorized.

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(c) Folic acid and neural tube defects (insert cite and date of publication in the **Federal Register** of the final rule).

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

[FR Doc. 91-27167 Filed 11-26-91; 8:45 am]

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21 CFR Part 101

[Docket No. 91N-0101]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements; Antioxidant Vitamins and Cancer

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing not to authorize the use on foods, including dietary supplements, of health claims relating to the association between antioxidant vitamins and cancer. FDA has reviewed the authoritative documents and scientific data in conformance with the requirements of the Nutrition Labeling and Education Act (the 1990 amendments) and concluded that there is not significant scientific agreement to support the use of health claims relating to antioxidant vitamins and cancer on labels and labeling. Although scientific evidence is suggestive of an effect of beta-carotene on cancer risk, studies available to date have been based on consumption of fruit and vegetables high in beta-carotene and not beta-carotene itself. Clinical trials are currently underway to clarify