TIME AND DATES: 2:18 p.m., October 8, 1993.
PLACE: Conference Room, 1333 H Street, NW, Suite 300, Washington, DC 20268.
STATUS: Closed.
MATTERS TO BE CONSIDERED: Personnel Matters.
CONTACT PERSON FOR MORE INFORMATION: Charles L. Clapp, Secretary, Postal Rate Commission, Suite 300, 1333 H Street, NW, Washington, DC 20268–0001, Telephone (202) 789–6840.

Charles L. Clapp,
Secretary.
[FR Doc. 93–25394 Filed 10–12–93; 2:58 pm]
BILLING CODE 7710–FW–P

POSTAL RATE COMMISSION

TIME AND DATES: 2:07 p.m., October 8, 1993.
PLACE: Conference Room, 1333 H Street, NW, Suite 300, Washington, DC 20268.
STATUS: Open.
MATTERS TO BE CONSIDERED: Election of Vice Chairman.
CONTACT PERSON FOR MORE INFORMATION: Charles L. Clapp, Secretary, Postal Rate Commission, Suite 300, 1333 H Street, NW., Washington, DC 20268–0001, Telephone (202) 789–6840.

Charles L. Clapp,
Secretary.
[FR Doc. 93–25395 Filed 10–12–93; 3:00 pm]
BILLING CODE 7710–FW–P

U.S. RAILROAD RETIREMENT BOARD

Notice of Public Meeting

Notice is hereby given that the Railroad Retirement Board will hold a meeting on October 19, 1993, 9:00 a.m., at the Board's meeting room on the 8th floor of its headquarters building, 844 North Rush Street, Chicago, Illinois, 60611. The agenda for this meeting follows:

Portion open to the public

(1) Plan to Improve the Quality and Timeliness of Claims Processing
(2) Debt Prevention Task Force Report
(3) Pre-Recovery Waiver Debt
(4) Request for Waiver of Interest and/or Penalty Assessments
(5) Division of Audit and Compliance Fiscal Year 1993 Audit Plan
(6) Announcement No. 93–17A GM–13 Audit Manager
(7) 1993 Railroad Retirement Board Award for Excellence Program
(8) Performance Awards for General Schedule Employees
(9) RRB Physical Examination Program
(10) Updated Energy Conservation Program
(11) Coverage Determination—Livingston Rebuild Center
(12) Coverage Determination—Parker LaFarge, Inc.
(13) Coverage Determination—Kokomo Rail Company, Inc.
(14) Coverage Determination—VWV Enterprises, Inc.
(15) Coverage Determination—Rio Grande Industries, Inc.
(16) Coverage Determination—Illinois Central Corporation
(17) Coverage Determination—Rail Link, Inc.
(18) Coverage Determination—Albany Bridge Company, Inc.
(19) Coverage Determination—Tulare Valley Railroad Company
(20) Coverage Determination—Reading and Northern Service Company
(21) Coverage Determination—Santa Cruz, Big Trees & Pacific Ry. Co.
(22) Regulations—Parts 202 and 301, Employers Under the Railroad Retirement Act and Railroad Unemployment Insurance Act
(23) Regulations—Part 203, Employees Under the Railroad Retirement Act
(24) Regulations—Part 226, Computing Employee Spouse and Divorced Spouse Annuities
(25) Regulations—Part 230, Reduction and Non—Payment of Annuities by Reason of Work
(26) Regulations—Part 266, Representative Payee
(27) Regulations—Part 328, Voluntary Leaving of Work
(28) Regulations—Part 345, Contribution and Contribution Reports

Portion closed to the public

(A) Draft Fiscal Year 1994 Performance Appaisal Plans
(B) Appeal of Nonwaiver of Overpayment, Willard H. Triplett

The person to contact for more information is Beatrice Ezerski, Secretary of the Board, COM No. 312–751–4920, FTS No. 386–4920.

Dated: October 8, 1993.

Beatrice Ezerski,
Secretary to the Board.
[FR Doc. 93–25307 Filed 10–12–93; 9:48 am]
BILLING CODE 7905–01–M

Corrections

Federal Register
Vol. 58, No. 197
Thursday, October 14, 1993

This section of the FEDERAL REGISTER contains editorial corrections of previously published Presidential, Rule, Proposed Rule, and Notice documents. These corrections are prepared by the Office of the Federal Register. Agency prepared corrections are issued as signed documents and appear in the appropriate document categories elsewhere in the issue.

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 90

[PR Docket No. 90-481; FCC 93-411]

Construction, Licensing and Operation of Private Land Mobile Radio Stations

Correction

In rule document 93-23785, beginning on page 51251 in the issue of Friday, October 1, 1993, make the following correction:

On page 51251, in the second column, in the **EFFECTIVE DATE:** , in the first line, "October 1, 1993." should read "November 1, 1993."

BILLING CODE 1505-01-D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 812

[Docket No. 92N-0308]

Investigational Device Exemptions; Disqualification of Clinical Investigators

Correction

In proposed rule document 93-24475 beginning on page 52144 in the issue of Wednesday, October 6, 1993, make the following correction:

On page 52144, in the first column, in **DATES:**, in the first and second lines, "November 5, 1993." should read "December 6, 1993."

BILLING CODE 1505-01-D

federal register

Thursday
October 14, 1993

Part II

Department of Health and Human Services

Food and Drug Administration

Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93N–0173]

Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is making available, through this document, a statement of the manner in which FDA's current statutory authorities governing therapeutic products apply to human somatic cell therapy products and gene therapy products. FDA is publishing this statement in response to requests that the agency clarify its regulatory approach and provide guidance to manufacturers of products intended to be used in somatic cell therapy or gene therapy. As scientific knowledge in the area of somatic cell and gene therapy continues to accumulate and evolve, the agency's approach may also evolve.

DATES: Submit written comments on the document by December 13, 1993.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Submit investigational new drug applications (IND's) for somatic cell therapy and gene therapy products to the Division of Application Review and Policy (HFM–585), Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Submit written requests for single copies of the document entitled "Points to Consider in Human Somatic Cell Therapy and Gene Therapy" to the Congressional and Consumer Affairs Branch (HFM–12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–295–9000. Send two self-addressed adhesive labels to assist that office in processing requests.

FOR FURTHER INFORMATION CONTACT: Ann Reed Gaines, Center for Biologics Evaluation and Research (HFM–635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

As a consequence of scientific and biotechnological progress during the past decade, new therapies involving somatic cells and genetic material are being investigated, and commercial development of products for use in somatic cell therapies and gene therapies is occurring. Existing FDA statutory authorities, although enacted prior to the advent of somatic cell and gene therapies, are sufficiently broad in scope to encompass these new products and require that areas such as quality control, safety, potency, and efficacy be thoroughly addressed prior to marketing. Manufacturers and other interested parties have questioned FDA regarding how such products will be regulated. This statement outlines the current regulatory approach to products intended for use in somatic cell and gene therapies.

II. Background

A. Legal Authorities

FDA regulates numerous kinds of products intended to prevent, treat, or diagnose diseases or injuries under legal authorities established in the Public Health Service Act (the PHS Act) and the Federal Food, Drug, and Cosmetic Act (the act). Section 351(a) of the PHS Act (42 U.S.C. 262(a)) identifies a biological product as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man." Section 201(g)(1) of the act (21 U.S.C. 321(g)(1)) defines the term "drug," in part, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." The term "device" is defined in section 201(h) of the act, in part, as:

> * * * "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article * * * intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, * * * which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

Both the "drug" definition and the "device" definition also include articles "intended to affect the structure or any function of the body."

Section 351(a) of the PHS Act requires premarket approval for biological products. Licenses are to be issued upon a showing that the establishments and products "meet standards, designed to insure the continued safety, purity, and potency of such products * * *." (42 U.S.C. 262(d)). A biological product's effectiveness for its intended uses must be shown as part of the statutory requirement for potency (21 CFR 600.3(s)). At the investigational stages, when the products are being studied in clinical trials to gather safety and effectiveness data, biological products must meet the requirements of part 312 (21 CFR part 312). FDA's biologics regulations require the submission of both product license applications (PLA's) and establishment license applications (ELA's) (21 CFR 601.1 through 601.10). Biologics establishments and products must satisfy detailed standards set forth in the regulations (21 CFR parts 600 through 680).

Section 351(b) of the PHS Act prohibits falsely labeling or marking a biological product. Under section 361 of the PHS Act (42 U.S.C. 264), the agency may promulgate regulations to prevent the introduction, transmission, or spread of communicable diseases.

Products considered to be biological products subject to the provisions of section 351 of the PHS Act are simultaneously also drugs or devices subject to the applicable provisions under the act. For example, the adulteration, misbranding, and registration provisions of the act would apply to the product as a drug or device.

Under section 501 of the act (21 U.S.C. 351), both drugs and devices are considered adulterated for any of a number of specified reasons. Included among these adulteration provisions is the requirement that the methods and facilities and controls used for manufacture, processing, packing, and holding or installation conform with current good manufacturing practice (CGMP) regulations (21 U.S.C. 351(a)(2)(B) and (h)). FDA's implementing regulations codified at 21 CFR parts 211 and 820 specify the drug and device CGMP requirements.

Section 502 of the act (21 U.S.C. 352) sets forth misbranding provisions that apply to drugs and devices. Among other circumstances, a drug or device is considered misbranded if the labeling is false or misleading or if the labeling fails to bear adequate directions for use or adequate warnings against unsafe use (21 U.S.C. 352(a) and (f)). Any drug or device is also misbranded if it is dangerous to health when used in the manner or with the frequency suggested in the labeling (21 U.S.C. 352(j)). For prescription drugs and restricted

devices, section 502 of the act describes certain information that must be included in all advertisements or other printed material (21 U.S.C. 352(n) and (r)). FDA's regulations also establish labeling and advertising requirements in more detail (21 CFR parts 201, 202, and 801).

Section 510 of the act (21 U.S.C. 360) requires persons who own or operate establishments for the manufacture, preparation, propagation, compounding, or processing of drugs or devices (with certain exceptions) to register those establishments with FDA. Individuals who must register their establishments under section 510 of the act must also file a list of all the drugs and devices being made or processed at the establishment. FDA's registration regulations are codified at 21 CFR parts 207 and 807.

Although products regulated by FDA as biological products must also meet drug or device requirements, the agency does not require duplicate premarket approvals. For example, if FDA requires a PLA to be submitted for the product as a biologic, the agency does not also require submission of a new drug application (NDA) or a device premarket approval application (PMA).

The interstate commerce nexus needed to require premarket approval under the statutory provisions governing biologics and drugs may be created in various ways in addition to shipment of the finished product by the manufacturer. For example, even if a biological drug product is manufactured entirely with materials that have not crossed State lines, transport of the product into another State by an individual patient creates the interstate commerce nexus. If a component used in the manufacture of the product moves interstate, the interstate commerce prerequisite for the prohibition against drug misbranding is also satisfied even when the finished product stays within the State. Products that do not carry labeling approved in a PLA (or NDA) are misbranded under section 502(f)(1) of the act (21 U.S.C. 352(f)(1); 21 CFR 201.5, 201.100(c)(2)). Moreover, falsely labeling a biological product is prohibited under section 351(b) of the PHS Act without regard to any interstate commerce nexus (42 U.S.C. 262(b)). The act contains a presumption of interstate commerce for devices (section 709 of the act (21 U.S.C. 379a)).

Both the PHS Act and the act provide authority for enforcement of the various statutory requirements. FDA is authorized to conduct inspections to determine compliance with regulatory requirements (42 U.S.C. 262(c) and 21 U.S.C. 360(h) and 374). Approved PMA's may be suspended or revoked (42 U.S.C. 262(a) and 21 U.S.C. 355(e) and 360e(e)). Biological products and devices may be recalled under certain circumstances (42 U.S.C. 262(d)(2) and 21 U.S.C. 360h). Judicial actions, including seizures, injunctions, and criminal prosecutions, may also be initiated (42 U.S.C. 262(f) and 21 U.S.C. 332, 333, and 334).

Some products may contain a combination of biological products and drugs or devices. Under a provision of the Safe Medical Devices Act of 1990, FDA determines the primary mode of action of the combination products (21 U.S.C. 353(g)), then assigns the primary jurisdiction for review of the product within the agency based on that determination. FDA has established procedures for designating the organization within FDA (i.e., the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH)) to review combination products or any other products where the agency center with primary jurisdiction is unclear (21 CFR 3.1 through 3.10). CBER, CDER, and CDRH have also entered into intercenter agreements to clarify the centers' responsibilities for reviewing various kinds of products.

B. Regulation of Somatic Cell and Gene Therapy Products

This statement is intended to present the agency's current approach to regulating somatic cell and gene therapy products. For the purpose of this statement, somatic cell therapy products are defined as autologous (i.e., self), allogeneic (i.e., intra-species), or xenogeneic (i.e., inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries. Cellular products intended for use as somatic cell therapy are biological products subject to regulation pursuant to the PHS Act (42 U.S.C. 262) and also fall within the definition of drugs in the act (21 U.S.C. 321(g)). As biological products, somatic cell therapy products are subject to establishment and product licensure to ensure product safety, purity, and potency. At the investigational stage, these products must be in compliance with part 312. Clinical trials are, therefore, to be conducted under IND's. As drugs, somatic cell therapy products are also subject to drug requirements such as conformity with CGMP regulations.

FDA has not required premarketing approval for many types of transplantation, including bone marrow transplants. However, recent scientific and biotechnological developments now enable bone marrow to be manufactured into a somatic cell therapy product. Such products are subject to FDA regulation consistent with the approach to other somatic cell therapies described in this statement. In addition, other forms of transplantation, such as the transfer of whole organs and tissues, have been, or are currently being reassessed and addressed by FDA or other Federal agencies in light of current knowledge and technological advances.

Gene therapy products are defined for the purpose of this statement as products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells. Some gene therapy products (e.g., those containing viral vectors) to be administered to humans fall within the definition of biological products and are subject to the licensing provisions of the PHS Act, as well as to the drug provisions of the act. Other gene therapy products, such as chemically synthesized products, meet the drug definition but not the biological product definition and are regulated under the relevant provisions of the act only.

Biological products intended for use as source materials for further manufacture into licensed somatic cell therapy products or gene therapy products require premarketing approval as biological products intended for further manufacture when they are shipped from one legal entity to another. Such products would be considered part of a shared manufacturing arrangement in which: (1) Two or more manufacturers perform different aspects of the manufacture of a product, (2) neither performs nor is licensed to perform all aspects of the manufacture, and (3) each manufacturer holds product and establishment license applications. In a shared manufacturing arrangement, FDA accepts only license applications for biological products intended for further manufacture that specify the licensed manufacturer or manufacturers to which the intermediate product will be shipped and approves such applications only after demonstration of safety and efficacy of the end product. For example, biological gene therapy products intended for use ex vivo in the manufacture of genetically altered cells for somatic cell therapies will require premarketing approval as biological

products intended for further manufacture when shipped from one legal entity to another and will be approved only when the final somatic cell therapy product is approved. For further discussion regarding shared manufacturing, refer to FDA's policy statement concerning cooperative manufacturing arrangements for licensed biological products, which was published in the **Federal Register** on November 25, 1992 (57 FR 55544).

In accordance with the statutory provisions governing biological products and drugs, a somatic cell therapy product or gene therapy product must be the subject of an IND in compliance with part 312 or of an approved PLA regardless of whether the finished product is shipped across State lines.

The manufacture of somatic cell therapy products or gene therapy products will involve many ancillary products used as part of the manufacturing process. The ancillary products are not intended to be present in final products but may have an impact on the safety, purity, or potency of the products under manufacture. Such ancillary products meet the definition of devices and, if marketed, will be regulated under the act device authorities, with the appropriate type of regulatory control being determined according to codified procedures (e.g., investigational device exemption (IDE)—21 CFR part 812; premarket approval (PMA)—21 CFR part 814; premarket notification (510(k))—21 CFR 870.81 through 807.97). When these ancillary products are used in the manufacturing of somatic cell or gene therapy products, they become subject to drug CGMP's, in particular for components and containers (21 CFR 211.80 through 211.94 and 211.101(b) and (c)).

Some of the ancillary products will already be marketed as medical devices, drugs, or biological products. When an ancillary product used as a component of the manufacturing process is marketed but not labeled for the specific use, such use may initially be described under the IND for the final somatic cell or gene therapy product. Such use of ancillary products by manufacturers of investigational somatic cell therapy or gene therapy products is contingent upon the submission of complete descriptions of the use of the ancillary product in the manufacturing process.

If the ancillary product used as a component of the manufacturing process does not have marketing approval, manufacturers of the somatic cell or gene therapy product must submit or provide cross-reference to a complete description of the manufacturing process, specifications, qualification, and acceptance criteria of the ancillary product. This information may be filed by the sponsor of the IND for the somatic cell or gene therapy product, may be filed in an IND or IDE by the manufacturer of an ancillary product, or may be made available by the manufacturer of the ancillary product in a master file format, as defined in 21 CFR 814.3(d) and discussed in 21 CFR 814.20(c).

Manufacturers who wish to market ancillary products for use in the manufacturing of somatic cell or gene therapy products must file either: (1) A 510(k), (2) a PMA, (3) an amendment to an existing 510(k), PMA, NDA, or PLA.

The manufacture of somatic cell therapy products or gene therapy products may involve components of manufacture intentionally present as part of the final products. Products containing both a somatic cell component and another drug or device component in the final product will be handled as combination products.

The following statement succinctly describes FDA's current approach to regulating somatic cell therapy and gene therapy products with primary emphasis on premarket approval issues. As previously discussed, products that meet the biologic, drug, or device definition must also comply with other relevant provisions of the PHS Act and the act. Manufacturers may also find useful information in FDA's document entitled "Points to Consider in Human Somatic Cell Therapy and Gene Therapy," Docket No. 91N–0428, available from CBER's Congressional and Consumer Affairs Branch (address above).

III. Statement

A. Somatic Cell Therapy

1. Definition

Somatic cell therapy is the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans by the administration of autologous, allogeneic, or xenogeneic cells that have been manipulated or altered ex vivo. Manufacture of products for somatic cell therapy involves the ex vivo propagation, expansion, selection, or pharmacologic treatment of cells, or other alteration of their biological characteristics.

2. Cells Subject To Licensure as Final Products When Intended for Use as Somatic Cell Therapy

Cells subject to licensure as final biological products when intended for use as somatic cell therapy include cells manipulated in a way that changes the biological characteristics of the cell population (e.g., by expansion, selection, encapsulation, activation, or genetic modification as a part of gene therapy as defined in section III.B.1. of this document).

Examples include the following: (1) Autologous or allogeneic lymphocytes activated and expanded ex vivo (e.g., lymphokine-activated killer cells (LAK), tumor infiltrating lymphocytes (TIL cells), antigen specific clones); (2) encapsulated autologous, allogeneic, or xenogeneic cells or cultured cell lines intended to secrete a bioactive factor or factors (e.g., insulin, growth hormone, a neurotransmitter); (3) autologous or allogeneic somatic cells (e.g., hepatocytes, myocytes, fibroblasts, bone marrow- or blood-derived hematopoietic stem cells, lymphocytes) that have been genetically modified; (4) cultured cell lines; and (5) autologous or allogeneic bone marrow transplants using expanded or activated bone marrow cells. (For bone marrow products whose status is not clear, consult CBER.)

3. Cells and Tissues Subject to Licensure as Source Material

Cells and tissues subject to biological product licensure as source material include allogeneic or xenogeneic cells harvested by other than the final product license holder and intended for manufacture into a somatic cell product. Examples include the following: (1) Muscle cells removed from donors and shipped to a manufacturer for expansion into a muscle cell therapy, (2) animal cells harvested at an animal care facility and shipped to a manufacturer for encapsulation or other manufacturing steps into a somatic cell therapy, and (3) other human tissue harvested from donors and shipped to another legal entity for manufacture into a somatic cell therapy.

4. Cells for Which Applications for Approval Prior to Marketing are not Presently Required

Cells for which applications for approval prior to marketing are not required at the present time include the following: (1) Cell transplants not having the characteristics described in sections III.A.2. and III.A.3. of this document, and (2) minimally manipulated or purged bone marrow transplants. Examples include the following: (1) Allogeneic bone marrow transplantation employing ex vivo T cell purging with a monoclonal antibody approved for such purging, (2) autologous bone marrow transplantation employing ex vivo tumor cell purging by an approved agent, and (3)

autologous bone marrow transplantation employing bone marrow enriched for stem cells by immunoadherence. (However, extensive manipulation of bone marrow for the purpose of obtaining purified stem cell populations would result in a somatic cell therapy subject to licensure.)

B. Gene Therapy

1. Definition

Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified ex vivo for subsequent administration or may be altered in vivo by gene therapy products given directly to the subject. When the genetic manipulation is performed ex vivo on cells that are then administered to the patient, this is also a type of somatic cell therapy. The genetic manipulation may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans.

2. Final Products Containing the Genetic Material Intended for Gene Therapy

Final products containing the genetic material intended for gene therapy are regulated as biological products requiring PLA's (e.g., viral vectors containing genetic material to be transferred, ex vivo transduced cells and analogous products) or as drugs requiring NDA's (e.g., synthetic products) regardless of whether they are intended for use in vivo or ex vivo. Gene therapy products that are licensed biological products will be approved as biological products intended for further manufacture if they are intended to be used ex vivo during the manufacture of genetically altered cells.

Examples include the following: (1) A synthetic polynucleotide sequence intended to alter a specific genetic sequence in human somatic cells after systemic administration is regulated as a drug requiring an NDA; (2) a retroviral vector containing the adenosine deaminase (ADA) gene, intended to be administered intravenously to the patient, is regulated as a biological product requiring a PLA; and (3) a retroviral vector containing the ADA gene and intended to modify cells ex vivo is regulated as a biological product intended for further manufacture requiring a PLA.

3. Viral Vector Systems Intended for Further Manufacture Into Final Products

The manufacture and quality control of viral vector systems (i.e., not containing the complete genetic material) that are designed to serve as the starting point for further manufacture into final products (i.e., insertion of additional genetic material into the vector) may be described in a drug master file.

C. Ancillary Products Used during Production of Somatic Cell Therapies

Numerous products will be used during production of somatic cell therapy. Examples include the following: (1) Bioreactors and cell culturing systems, (2) components of culture media, (3) drug- or biologic-like components used to activate or otherwise change the biological characteristics of the cells, (4) certain antisense polynucleotides, and (5) agents used to purge or select or stimulate specific cell populations. A common characteristic of these products is that they are intended to act on the cells, rather than to have an independent effect on the patient. Additionally, the intended action of these products is not dependent upon incorporation into the somatic cell with maintenance of the products' structural or functional integrity.

These products meet the definition of medical devices. They are regulated as devices, with the type of regulatory control being determined according to codified procedures. In contrast, products administered directly to patients or products whose function requires incorporation into the somatic cells with maintenance to some degree of structural or functional integrity (e.g., viral or other vectors containing genetic material to be used in gene therapy) are not considered ancillary products; rather, they are regulated as drugs or biological products.

The center primarily responsible for regulating a particular device will be designated according to the current intercenter agreements. For example, according to the current agreement, CDER will regulate the synthetic antisense compounds, CBER will be responsible for monoclonal antibody-based purging agents, and CDRH will oversee the approval of bioreactors.

D. Combination Products

Many somatic cell products administered to patients will be combinations of a biological product and a device or of a drug, a biological product, and a device. Examples include the following: (1) Encapsulated pancreatic islet cells secreting insulin, and (2) a device containing encapsulated cells secreting a neurotransmitter. The combination products for which the primary mechanism of action is that of the somatic cell therapy component will be regulated as biological products.

IV. Comments

FDA recognizes that somatic cell and gene therapy products constitute a new and emerging scientific area. The agency will review and consider written comments on the regulatory approach set forth in this notice. Any comments received will be considered in determining whether amendments to, or revisions of, the approach are warranted. Two copies of any comments should 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. Comments received are available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 24, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy

[FR Doc. 93–24938 Filed 10–13–93; 8:45 am]

BILLING CODE 4160–01–F

federal register

Thursday
October 14, 1993

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 101, et al.
Folic Acid; Proposed Rules

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 91N–100H]

RIN 0905–AB67

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

AGENCY: Food and Drug Administration, DHHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise its food labeling regulations to authorize the use of a health claim about the relationship between folate and the risk of neural tube birth defects on labels or in labeling of foods in conventional food form or dietary supplements. This rule is being proposed in response to provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) and the Dietary Supplement Act of 1992 (the DS Act) that bear on health claims. FDA has reviewed the scientific data in conformity with the requirements of the 1990 amendments and has considered recommendations provided by the Folic Acid Subcommittee of its Food Advisory Committee (the Folic Acid Subcommittee) as well as comments received. The agency has tentatively decided to authorize a health claim for folate and neural tube defects (NTD's) and to provide for safe use of folic acid in foods by amending several of its regulations that permit use of folic acid in foods.

DATES: Written comments by December 13, 1993. The agency is proposing that any final rule that may issue based upon this proposal become effective 30 days after the date of publication, except that for foods that are fortified with folic acid to ensure that the folic acid is safely used, any final rule authorizing a health claim will not be effective until the effective date of the amendment to the food additive regulation for folic acid proposed elsewhere in this issue of the **Federal Register**.

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

FOR FURTHER INFORMATION CONTACT: Jeanne I. Rader, Center for Food Safety and Applied Nutrition (HFS–175), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–205–5375.

SUPPLEMENTARY INFORMATION:

I. Background

A. The 1990 Amendments

The 1990 amendments to the Federal Food, Drug, and Cosmetic Act (the act) provided for extensive changes in the way foods are labeled. With respect to health claims, the 1990 amendments amended the act by adding a provision (section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B))) that provides 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. Congress enacted the health claims provisions of the 1990 amendments to help U.S. consumers maintain healthy dietary practices and to protect consumers from unfounded health claims. The 1990 amendments required that FDA evaluate 10 nutrient-disease relationships with respect to their appropriateness for health claims. The topic of folic acid and NTD's was among those 10 topics.

In the **Federal Register** of November 27, 1991 (56 FR 60537), the agency proposed to establish general requirements in conformity with the requirements of the 1990 amendments that would govern the appropriateness and validity of health claims. On January 6, 1993, FDA published a final rule on the general requirements for health claims (58 FR 2478). The regulation that FDA adopted provides that the agency will promulgate regulations authorizing health claims only when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner that is consistent with generally recognized scientific procedures and principles), that there is significant agreement, among experts qualified by training or experience to evaluate such claims, that the claim is supported by the scientific evidence.

The regulation also requires, among other things, that all label and labeling statements about the substance-disease relationship be based on and be consistent with the conclusions set forth in the regulation (§ 101.14(d)(2)(i)(21 CFR 101.14(d)(2)(i)); that the claim be limited to describing the value that ingestion of the substance, as part of a total dietary pattern, may have on a particular disease or health-related condition (§ 101.14(d)(2)(ii)); that the claim be complete, truthful, and not misleading, and, where factors other than dietary intakes of the substance affect the relationship between the substance and the disease or health-related condition, such factors may be required to be addressed in the claim (§ 101.14(d)(2)(iii)); that all information required to be in the claim appear in one place without other intervening material (§ 101.14(d)(2)(iv)); that the claim enable the public to comprehend the information provided and to understand the relative significance of such information in the context of a total daily diet (§ 101.14(d)(2)(v)); and that the level of the substance be sufficiently high and in an appropriate form to justify the claim (§ 101.14(d)(2)(vii)). Foods bearing health claims must also bear nutrition labeling including information on the substance that is the subject of the health claim (§ 101.14(d)(3)).

The health claim provisions of the 1990 amendments do not alter the requirements of the act that foods be safe, and that information on food labels and labeling be truthful and not misleading. Sections added by the 1990 amendments cannot be implemented independently of the remaining portions of the act. The act must be considered as a whole, and FDA's responsibility for ensuring that foods are safe, and that labeling is not misleading, is explicitly provided for in sections 402 (21 U.S.C. 342) and 403 of the act. Further, a health claim cannot be authorized for a substance if its use would increase the risk of another disease or health-related condition, and disqualifying levels for sodium, total fat, saturated fat, and cholesterol cannot be exceeded in foods bearing health claims. Additional disqualifying provisions could be specified as appropriate.

B. The DS Act

The agency notes that the final rule on general requirements for health claims that it published January 6, 1993 (58 FR 2478), did not include general requirements for health claims on dietary supplements. In October 1992, Congress passed the DS Act (Pub. L. 102–571), which imposed a moratorium until December 15, 1993, on FDA implementation of the 1990 amendments with respect to dietary supplements not in conventional food form. The DS Act directed FDA to issue, by June 15, 1993, proposed rules to implement the 1990 amendments with respect to dietary supplements and to issue final rules based on these proposals by December 31, 1993. Accordingly, FDA published (58 FR 33700, June 18, 1993) a proposed rule on general requirements for health claims on dietary supplements. FDA proposed to revise its food labeling

regulations to make dietary supplements of vitamins, minerals, herbs, or other similar nutritional substances subject to the general requirements that apply to all other types of food with respect to health claims.

The DS Act also amended the so-called "hammer" provision of the 1990 amendments to provide that if the agency does not meet the established December 31, 1993, timeframe for issuance of final rules, the proposed regulations are to be considered final regulations.

With respect to the 10 nutrient-disease relationships that the 1990 amendments directed FDA to consider, in the **Federal Register** of January 6, 1993 (58 FR 2537 through 2849), the agency issued regulations announcing its decisions with respect to foods in conventional food form on each of these relationships. However, under section 202(a)(1) and (b) of the DS Act, while FDA could provide that the health claims that it authorized for food in conventional food form could also appear on dietary supplements that qualified to bear those claims, the agency could not act before December 15, 1993, to deny claims on dietary supplements on any of the 10 relationships.

In the wake of the January 6, 1993, final rules, six nutrient-disease relationships remain unresolved for dietary supplements. In this document, FDA is proposing to authorize a health claim on the relationship between folate and NTD's. This proposal pertains to all food, whether in conventional food form or a dietary supplement. Elsewhere in this issue of the **Federal Register**, FDA is addressing the remaining five nutrient-disease relationships for dietary supplements.

C. Chronology of Regulatory and Other Activities Related to Folate and NTD's

Since the passage of the 1990 amendments in November 1990, the rapidly evolving nature of the science relative to folate and NTD's and a number of Public Health Service (PHS) activities have intertwined with the regulatory process relative to a health claim for this topic. To facilitate an understanding of FDA's evolving activities on this matter, these events are described briefly in chronological order below and in greater detail later in this document.

1. The Proposed Rule

In response to the 1990 amendments, the agency proposed (56 FR 60610, November 27, 1991) not to authorize the use on the label or in labeling of foods, including dietary supplements, of health claims relating to an association between folic acid and NTD's.

a. *Summary of data.* In reaching this tentative decision, the agency reviewed all of the available human studies. These studies consisted of four intervention trials with women at high risk of recurrence of an NTD pregnancy because of a personal history of such a pregnancy (Refs. 1, 2, 3, and 4; Table 1) and four observational studies of women at risk of occurrence of an NTD pregnancy (Refs. 5, 6, 7, 8, and 9; Table 2). FDA also reviewed a number of studies in which levels of various vitamins were measured in blood samples obtained from women during or following the periconceptional interval (i.e., around the time of conception) and a number of animal studies to determine whether vitamin status was associated with risk for an NTD pregnancy (see 56 FR 60610). With the exception of the Medical Research Council of the United Kingdom (MRC) trial (Ref. 4) the results of these studies were not conclusive relative to a specific effect of folate intake on reduction in risk of pregnancies affected by NTD's.

In July 1991, the MRC (Ref. 4) published the results of a well-conducted clinical trial in which women at high risk of an NTD-affected pregnancy, because of a personal history of such a pregnancy, were given supplements containing 4 milligrams (mg) (4,000 micrograms (µg)) of folic acid daily (i.e., 10 times the Reference Daily Intake (RDI)), and the outcomes of their pregnancies were compared with those of women who had not received folic acid in their supplements. This study clearly demonstrated, for the first time, a significant reduction in recurrence of NTD's with high levels of folic acid but not with supplementation with other vitamins. This study established a specific role for folic acid in reducing the risk of recurrence of NTD pregnancies in women with a previous history of this defect, but extrapolation of these results to women in the general population at much lower risk of occurrence of NTD-affected pregnancies, and extrapolation of the results to lower levels of folate (e.g., 400 µg folic acid daily, or 100 percent of the RDI), were problematic.

b. *Recommendations for women at risk of recurrence of an NTD-affected pregnancy.* In August 1991, the Centers for Disease Control (CDC) published guidelines for use of folic acid at high intake levels (i.e., at 4 mg (4,000 µg or 10 times the RDI)) by those women who are planning a pregnancy and who are at high risk of a recurrence of an NTD-complicated pregnancy (Ref. 10). CDC recommended that women who had previously had a pregnancy resulting in a fetus or an infant with a NTD should be counseled about the increased risk of such a complication in subsequent pregnancies and should be advised that folic acid supplementation may reduce the risk of a recurrence. The guidelines stated that such women should consult their physician when planning a pregnancy and, unless contraindicated, should be advised to take 4 mg (4,000 µg) of folic acid daily beginning at least 4 weeks before conception and continuing through the first 3 months of pregnancy (Ref. 10). The guidelines did not specifically address the issue of folate consumption among these women during the times when they were not planning to become pregnant or among women who did not have a history of an NTD-affected pregnancy.

FDA, in its proposed rule published in the **Federal Register** of November 27, 1991 (56 FR 60610), restated significant portions of the August 1991 CDC recommendation and noted the significance of this guideline for women at high risk of a recurrence of an NTD-affected pregnancy. The agency tentatively decided, however, not to authorize a health claim on the relationship between folic acid and NTD's. The agency noted that the amount of folic acid needed for reduction in risk of recurrence of NTD's in women at high risk of this complication is significantly in excess of usual dietary intakes and exceeds amounts permitted under current food additive regulations. In addition, the agency tentatively concluded that there was not significant agreement among qualified experts that intakes of folic acid lower than the level of 4 mg (4,000 µg) per (/) day used in the MRC trial would have the same protective effect as intake of the study dose of 4 mg/day. Additionally, at that time, there was not significant agreement among qualified experts that intakes of folic acid lower than those studied in this recurrence intervention trial, and consistent with current food additive regulations, would have the same effect in women in the general U.S. population, who are at much lower risk of an occurrence of an NTD-affected pregnancy than were the women at high recurrent risk who participated in the MRC study (56 FR 60610).

2. Reopening of the Comment Period

Subsequent to publication of the proposed regulation (56 FR 60610, November 27, 1991) and after the period for submitting comments in response to the proposal closed on February 25, 1992, FDA became aware of the possibility of significant new data on

folate and NTD's. Therefore, in the **Federal Register** of July 23, 1992 (57 FR 32751), the agency reopened the comment period to permit the inclusion of any new scientific data and information, particularly information that might become available as a result of a meeting on folic acid and NTD's that was to be held at CDC on July 27, 1992. The reopening of the comment period also provided an opportunity for the public to comment on that scientific data and information.

a. *New data.* As a result of the reopening of the comment period, preliminary data from a randomized, controlled trial that was conducted in Hungary (hereafter referred to as "the Hungarian study") of the effectiveness of multivitamin and multimineral supplements providing daily intakes of 0.8 mg (800 µg) of folic acid (i.e., twice the RDI) in reducing the risk of occurrence of NTD's became publicly available (58 FR 2606, Ref. 30). The agency also received information on the results of a case-control study of periconceptional use of multivitamins containing folic acid at daily doses of 0.4 mg (400 µg) and higher and the risk of occurrence of NTD's in women in Boston, Philadelphia, and Toronto (58 FR 2606, Ref. 31).

b. *PHS recommendation.* In September 1992, while FDA's rulemaking was in progress, the PHS (Ref. 11) issued a recommendation that all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg (400 µg) of folic acid/day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTD's. The recommendation was based on data suggesting that folic acid, when given at a high dose (4 mg or 4,000 µg), can reduce the risk of recurrence of NTD's (Ref. 4) and on a synthesis of information from studies that used multivitamins containing folic acid at dose levels from 0 to 1,000 µg/day can. Based on information provided in these studies, PHS inferred that folate alone at levels of 0.4 mg (400 µg)/day can reduce the risk of NTD's in some women. The PHS recommendation identified three approaches to delivering folate to women of childbearing age in the general population, including improvements in dietary habits, daily use of folic acid supplements throughout the childbearing years, and fortification of the U.S. food supply.

The PHS recommendation also identified several issues that remained outstanding. Among these issues were: (1) The appropriate intake of folate for reduction in risk of NTD's; (2) the potential role of other nutrients in reduction in risk of NTD's; (3) the "folate-preventable" fraction of NTD-affected pregnancies in women in the U.S. population; and (4) safety concerns, including effects of increased folate intakes in complicating the diagnosis of vitamin B_{12} deficiency if the food supply were to become highly fortified with folic acid. The PHS statement also noted that because the effects of high intakes of folate are not well known, but include complicating the diagnosis of vitamin B_{12} deficiency, care should be taken to keep total folate consumption at less than 1 mg (1,000 µg)/day except under the supervision of a physician (Ref. 11).

The target population for this recommendation includes about 70 million women of childbearing age in the United States throughout the approximately 30 years in which they are capable of becoming pregnant. The Department of Health and Human Services (DHHS)/PHS report estimated that about a 50-percent reduction in NTD births could occur if all women of childbearing age consumed 0.4 mg (400 µg) folic acid daily throughout their childbearing years (Ref. 11).

3. The Folic Acid Subcommittee

Given the seriousness of NTD's and the safety and other concerns stated in the PHS recommendation, the agency decided that it needed expert advice in deciding whether to authorize a health claim on folate and NTD's and in resolving certain separate but related issues involving the safety of folic acid. The agency convened the Folic Acid Subcommittee to consider the outstanding issues on folic acid (57 FR 52781, November 5, 1992). The Folic Acid Subcommittee had its first meeting on November 23 and 24, 1992 (Ref. 12). The agency asked the Folic Acid Subcommittee to provide recommendations on several issues, including identification of the appropriate target population for a folate–NTD's health claim, the appropriate daily intake of folate to reduce the risk of NTD's, safety concerns for the target population and the general population, and appropriate methods for presenting a health claim, if one is to be authorized, to the target population. The Folic Acid Subcommittee evaluated these issues in the broadest public health context and provided the agency with recommendations on educational activities for health professionals as well as for the target population, the need for surveillance both for changes in incidence of NTD's and for adverse effects of increased folate intake, labeling of foods (including health claims), and fortification of the food supply with folic acid. The Folic Acid Subcommittee, however, was unable to resolve all of the issues at its November 1992 meeting, particularly those involving food fortification.

4. The Final Rule

The 1990 amendments required that, within 2 years of their passage, FDA publish final regulations on the 10 nutrient-disease relationships. Therefore, in the **Federal Register** of January 6, 1993 (58 FR 2606), the agency published a final rule on a health claim for folic acid and NTD's. The agency did not authorize a health claim for folic acid and NTD's at that time. The agency reaffirmed its support of the PHS recommendation that all women of childbearing age in the United States who are capable of becoming pregnant consume 0.4 mg of folic acid daily to reduce their risk of having a pregnancy affected with spina bifida or other NTD's. The agency noted, however, that while the PHS recommendation evidenced that significant scientific agreement exists regarding the relationship between folate and NTD's, unresolved questions about the safe use of folic acid in food remained. The agency concluded that it could not authorize a health claim for folate until the questions regarding the safe use of this nutrient, as well as other concerns raised by PHS, were satisfactorily resolved. The agency stated its intention to work expeditiously to try to resolve these issues, including a review of the recommendations of the Folic Acid Subcommittee.

On April 15, 1993, FDA reconvened the Folic Acid Subcommittee (Ref. 13). FDA updated the Folic Acid Subcommittee on work done by FDA staff on fortification models. FDA asked for clarification on what appeared to be an inconsistency in positions taken by the Folic Acid Subcommittee relative to health claims. (At the November 23 and 24, 1992, meeting, the Folic Acid Subcommittee supported the PHS recommendation but recommended against use of health claims). Following expressions of diverse opinions of the potential effectiveness of health claims as an educational tool and by close votes by subcommittee members, the Folic Acid Subcommittee supported FDA actions to propose to authorize a health claim and to propose to fortify cereal-grain products.

D. The Purpose and Scope of This Document

The sections above describe the significant, and in some cases,

conflicting factors that the agency must consider in addressing the topic of folate and NTD's. In trying to resolve these conflicts, the agency has posed a series of questions for itself. These questions, and the agency's proposed answers, provide the basic outline for the remainder of this document.

The questions addressed by FDA include the following:

(1) Is a health claim on food labels appropriate for the relationship between folate and NTD's?

(2) Should the food supply be fortified with folic acid to ensure that women have adequate folate intakes? If so, is it necessary to limit the foods to which folic acid can be added and the levels at which it can be added to specific foods?

(3) If there are to be limitations on the foods that can be fortified with folic acid, which foods are most appropriate for fortification and at what levels should they be fortified?

(4) If the agency concludes that a health claim can be safely implemented, what should such a claim say about folate and NTD's?

In this document, the agency is proposing to authorize a health claim relating diets adequate in folate to reductions in the risk of NTD-affected pregnancies. FDA has tentatively concluded, based on the totality of the scientific evidence, that there is significant scientific agreement among qualified experts supporting a relationship between folate and NTD's. The agency has also tentatively concluded that, based on its discussions with the Folic Acid Subcommittee and its analyses of food intake data, daily folate intakes can be maintained within safe ranges by allocating fortification with folic acid to specific foods in the food supply through an amendment to the food additive regulation for folic acid.

In companion documents published elsewhere in this issue of the **Federal Register**, the agency is proposing to amend the food additive regulation for folic acid and to amend the standards of identity for specific cereal-grain products. The agency will seek specific comment on the companion proposals and on this proposal from the Folic Acid Subcommittee, the experts who participated in the November 23 and 24, 1992, meeting, and the agency's Food Advisory Committee. After the advisory committee meets, the agency will make these comments available for public review and comment, as part of this rulemaking, as soon as possible. FDA encourages public comment on the views that it receives from these experts.

II. Regulatory History of Folic Acid

FDA regulates folic acid as a drug or as a food additive, depending upon its intended use.

A. The Drug Regulation

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

The agency found that in the presence of excess folic acid and inadequate vitamin B_{12}, the anemia of vitamin B_{12} deficiency, which is generally the earliest indicator of the deficiency, may not develop (i.e., may be masked), thus delaying the diagnosis of the deficiency. Other serious consequences of the deficiency (e.g., severe and often irreversible neurologic damage), however, may progress and worsen because of the failure to detect the anemia at an early stage of the deficiency and initiate appropriate therapy with vitamin B_{12}. This interaction between the functions of folic acid and vitamin B_{12} (i.e., the ability of folic acid to mask the anemia of vitamin B_{12} deficiency) has been recognized for many years and is the basis for the precautionary statement on oral and parenteral preparations of folic acid for therapeutic use. In the final rule, the agency stated the conditions under which it would approve new drug applications for folic acid preparations (36 FR 6843). The labeling conditions included the following precaution: "Folic acid especially in doses above 1.0 mg daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive."

In the **Federal Register** of October 17, 1980 (45 FR 69043 at 69044), the agency amended the "Precautions" statement to be included in the labeling of oral and parenteral preparations of folic acid for therapeutic use in treating patients with megaloblastic anemia of folate deficiency, because the agency found that the revision more accurately stated the level at which folic acid may obscure pernicious anemia. The agency stated: "While obscuration of pernicious anemia does not occur at levels of 0.1 mg of folate/day, hematologic remissions in pernicious anemia have been reported at levels as low as 0.25 mg of folate per day." The precautions section of the labeling conditions for folic acid was amended to read as follows: "Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations remain progressive."

B. The Food Additive Regulation

In the **Federal Register** of August 2, 1973 (38 FR 20725), FDA published a final rule establishing safe conditions of use for folic acid (folacin) in food (§ 121.1134 (21 CFR 121.1134)). In determining the safe conditions of use for folic acid, the agency considered the Recommended Dietary Allowance (RDA) established by NAS and other relevant information. In 1977, § 121.1134 was recodified as § 172.345 (21 CFR 172.345).

The food additive regulation provides that folic acid can be added to foods if the maximum daily intake does not exceed 0.4 mg (i.e., 400 µg)/day for food labeled without reference to age or physiologic state. The regulation also includes limitations based on age and the conditions of pregnancy or lactation. Daily intake is not to 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 (§ 172.345). As currently written, however, this regulation provides no guidance to manufacturers as to how to reach the stated limit, and, as such, is inadequate to allocate folic acid safely in the food supply.

III. The Nature of the Relationship Between Folate and NTD's—Review of the Scientific Evidence

A. Background

1. Folates

The term "folates" is a generic descriptor for a group of compounds that have nutritional properties and chemical structures similar to those of pteroylglutamic acid (PGA, the parent form of the vitamins) (Ref. 14). Naturally-occurring folates in foods are in the reduced form (i.e., the dihydro or tetrahydro form) and are often conjugated to a number of glutamic acid residues (i.e., folylpolyglutamates). Synthetic folic acid added as a fortificant to foods, including dietary

supplements, is the oxidized, monoglutamate form of the vitamin.

During passage through the intestinal mucosa and liver, the reduced folylpolyglutamates found in foods are deconjugated (i.e., excess glutamic acid residues are removed) and converted to N^5-methyltetrahydrofolate, a reduced form with one methyl group that is the predominant circulating form of the vitamin in the serum and red blood cells. Folic acid (the oxidized, monoglutamate form of the vitamin), at low levels of intake, is also transported and reduced to the biologically active forms of the vitamin. Reduction of the oxidized folic acid is essential for its ability to function as a vitamin (i.e., to be involved in metabolic reactions involving one-carbon units) in human tissues (Ref. 14).

At median dietary intakes of above 200 µg/day, dietary folates are converted to the circulatory N^5-methyltetrahydrofolate form. The processes required to reduce and metabolize the vitamin can be saturated. At increasing levels of intake of synthetic folic acid, progressively more of the free vitamin circulates through the body in its oxidized form, and increasing amounts are excreted unmetabolized in the urine (Ref. 16).

As a vitamin, folate functions metabolically in the synthesis of amino acids and nucleic acids. Insufficient quantities of folate in the diet lead to impaired cell multiplication and alterations in protein synthesis (Ref. 15). These effects are most noticeable in rapidly growing or dividing cell populations (Ref. 15). Pregnancy increases the need for folate and many other nutrients because of the need of the mother to maintain adequate nutrition and to meet the nutritional requirements of the developing fetus (Ref. 15).

2. NTD's

NTD's are serious birth defects of the brain (e.g., anencephaly or absence of the forebrain and skull) or spinal cord (e.g., spina bifida or defective closure of the vertebrae around the spinal cord) that can result in infant mortality or serious disability. The neural tube forms between the 18th and 20th days of pregnancy and closes between the 24th and 27th days. The neural tube, therefore, forms and closes before most women are aware of their pregnancy.

Each year, NTD's occur in approximately 2,500 cases in the United States (i.e., in about 0.6/1,000 live births). During recent decades, the NTD rate in the United States has declined from 1.3/1,000 live births in 1970 to 0.6/1,000 live births in 1989 (Ref. 17). Factors that have contributed to this decline are not completely understood. Increased use of prenatal diagnosis and termination of pregnancy have been proposed as contributing factors; however, the declining trend in NTD's predates the widespread use of prenatal diagnosis (Ref. 18). The current U.S. rate of about 0.6/1,000 live births compares to rates of 2.8/1,000 in Hungary, 6.4/1,000 in Northern Ireland, and 6 to 13/1,000 in northern China. In 1989, spina bifida and anencephaly accounted for 533 infant deaths, or about 1.3 percent of all infant mortality in the United States. Although NTD's are not a major cause of infant mortality, they contribute significantly to life-long and often severe disabilities (Ref. 17).

The majority of NTD's are believed to have a multifactorial basis including both genetic and environmental factors. Environmental factors associated with NTD's include maternal health (e.g., febrile illness) (Ref. 19; and see 56 FR 60610), maternal use of certain antiseizure drugs (e.g., valproic acid, carbamazepine) (Ref. 20; and see 56 FR 60610), and environmental contaminants (Refs. 21 and 22). Another risk factor is a personal history of a pregnancy affected with an NTD (Ref. 23). Recurrence rates of 2 to 3 percent have been observed among U.S. women who have had a previous child with an NTD versus occurrence rates of about 0.06 percent in women in the general population. However, 90 to 95 percent of infants with an NTD are born to women who do not have a family history of these defects.

3. Relationship of Folates and NTD's

Several lines of evidence led to the hypothesis that nutritional factors might be involved in causing some cases of human NTD's (see 56 FR 60610, November 27, 1991, and 58 FR 2606, January 6, 1993 for references). Among the nutrients that were thought to play a role in the development of NTD's, folate, a B vitamin, received the greatest attention because of early observational studies in humans and because of the well-recognized role of folate in cell division and growth. Because the neural tube (the precursor of the brain and spinal cord) forms early in embryonic development (before the end of the 4th week of gestation), interventions aimed at reducing the risk of these defects must occur periconceptionally (i.e., during the interval extending from at least 1 month before conception and continuing through the first 6 weeks of pregnancy), often before a woman realizes that she is pregnant.

B. Review of the Scientific Evidence

Both in the November 27, 1991, proposed rule and in the January 6, 1993, final rule, the agency reviewed the totality of the publicly available scientific evidence on whether there is a relationship between folic acid and NTD's (see 56 FR 60610). Because of the agency's previous extensive reviews, only a brief overview of these studies will be provided here. Studies that became publicly available subsequent to publication of the final rule will also be reviewed.

Several different types of human studies have examined the relationship between folate and risk of NTD-affected pregnancies. The available human studies consist of several intervention trials and observational studies. In intervention trials (or clinical trials), the effects of periconceptional treatment with defined intakes of folic acid-containing supplements or placebos are compared in groups of subjects under controlled conditions. Observational studies, unlike intervention or clinical trials, do not compare the effects of defined treatments with the effects of a placebo. Rather, observational studies provide information on associations between an outcome or lack of an outcome (i.e., NTD's) and other factors (such as dietary intakes or supplement use) that differ between two outcome groups.

The populations in which studies of folate and NTD's have been performed have also varied. A number of intervention trials have examined the effects of periconceptional use of folic acid-containing supplements in women with a personal history of an NTD pregnancy because such women are at high risk of having another such pregnancy. Such trials are called *recurrence* trials. Studies with women in the general population without a personal history of an NTD pregnancy are called *occurrence* studies.

1. Intervention Trials in Women at Risk of Recurrence of NTD-Affected Pregnancies

Before 1991, three studies, two carried out in the British Isles and one carried out in Cuba, had suggested that supplementation with folic acid-containing multivitamins or with high levels of folic acid may reduce the risk of recurrence of NTD's in women at high risk of this complication. Two of these trials used high doses of folic acid (4 or 5 mg; 4,000 or 5,000 µg) daily and observed statistically nonsignificant trends in reduction in risk of NTD's (Refs. 1 and 3). The third trial showed a statistically significant beneficial

effect of a multivitamin supplement containing 0.36 mg (360 µg) of folic acid and vitamins A and D, thiamin, riboflavin, vitamin B_6, niacin, and vitamin C (see Table 1; Ref. 2).

In July 1991, the MRC published the results of a well-conducted randomized clinical trial in which women at high risk of a recurrence of an NTD-affected pregnancy, because of a personal history of such a pregnancy, were given supplements containing a high dose (i.e., 4 mg; 4,000 µg; 10 times the RDI) of folic acid with or without other vitamins daily (see 56 FR 60610 for review). The outcomes of their pregnancies were compared with those of women who had received identical supplements except for folic acid (Ref. 4). One thousand eight hundred seventeen women were recruited for this trial, of whom 1,195 subsequently had informative pregnancies (i.e., the outcome of the pregnancy with respect to the recurrence of an NTD in the fetus or infant was known). The great majority of patients in this study were from the United Kingdom or Hungary, areas with high occurrence rates of NTD's (e.g., 6.4/1,000 live births in Northern Ireland and 2.8/1,000 live births in Hungary). The data from this trial demonstrated that daily doses of 4 mg (4,000 µg) of folic acid before and during early pregnancy resulted in a 70 percent reduction in recurrence of NTD's in this group of high-risk women.

As stated above, this study clearly demonstrated, for the first time, a significant reduction in recurrence of NTD's with high levels of folic acid but not with other vitamins. This study established a specific role for folic acid in reducing the risk of recurrence of NTD pregnancies in women with a previous history of this defect, but extrapolation of these results to women in the general population at much lower risk and to lower levels of folate intake (i.e., 400 µg folate daily, or 100 percent of the RDI) was problematic. The level of folic acid used in the MRC trial, 4 mg (4,000 µg/day), is within the dose level regulated as a drug by FDA. The results of the MRC trial also showed that approximately 25 percent of NTD recurrences were resistant to folic acid supplementation, an observation that likely reflects the heterogeneous or multifactorial etiology of NTD's.

2. Intervention Trial in Women at Risk of Occurrence of NTD-Affected Pregnancies

In August of 1992, preliminary data from a randomized, controlled trial that was conducted in Hungary of the effectiveness of multivitamin and multimineral supplements providing daily intakes of 0.8 mg (800 µg) of folic acid (two times the RDI) in reducing the risk of occurrence of NTD's became publicly available (see 58 FR 2606) (Refs. 24 and 25). The rate of NTD's is 2.8/1,000 live births in Hungary.

In the Hungarian study (Ref. 24), women took multivitamin and multimineral preparations containing 0.8 mg (800 µg) of folic acid, 11 other vitamins, and 7 minerals (see Table 1). A control group of women took a placebo containing three trace minerals, calcium ascorbate (a source of vitamin C), and lactose (a sugar). Results of 4,156 pregnancies were reported. There were no occurrences of NTD's in the folic acid-containing multivitamin and multimineral group compared to 6 occurrences in the placebo group. At the time of closure of the trial, outcomes of several hundred pregnancies in both groups were unknown.

3. Observational Studies of Occurrence of NTD's

In developing its proposed rule, FDA reviewed the four available observational studies of associations between supplement use and risk for occurrence of NTD's (three case-control studies and one prospective cohort study) (56 FR 60610). The studies of Bower and Stanley (Ref. 8) and Milunsky et al. (Ref. 6) found statistically significant associations between reduced rates of NTD's and use of folic acid-containing multivitamin supplements during the periconceptional interval. The composition of the multivitamin supplements used in these studies was either undefined or, in one study (Ref. 6), the majority of preparations also contained vitamins A, C, D, or E in addition to folic acid (Table 2). These studies were unable to determine whether folic acid per se, other nutrients, or combinations of nutrients were specifically related to reduction in risk of NTD's. One study showed that timing of supplement use was important in that use of folic acid-containing supplements during the first 6 weeks of pregnancy was associated with a decreased incidence of NTD's, but no relationship was observed if use of the supplement was begun after 6 weeks of pregnancy (Ref. 6). This study also found from calculations of dietary folate intakes in nonsupplement users that dietary intakes of folate greater than 100 µg/day (0.1 mg) were associated with reduced risk of occurrence of NTD pregnancies. Conversely, one case-control study of more than 1,600 women carried out in areas of low prevalence of NTD's in the United States failed to support the findings of a positive effect against occurrence of these defects in women who consumed folic acid-containing multivitamin supplements or fortified breakfast cereals (Ref. 7).

In August 1992, the agency received information on the results of a case-control study of periconceptional use of multivitamins containing folic acid at daily doses of 0.4 mg (400 µg) and higher and the risk of occurrence of NTD's in women in Boston, Philadelphia, and Toronto (see 58 FR 2606). The results of this study in U.S. and Canadian populations were published in March 1993. The study (Ref. 26) covered 436 occurrent NTD cases and 2,615 control cases with other major malformations occurring between 1988 and 1991 in Boston, Philadelphia, and Toronto. Eight percent of cases (i.e., 35 cases) and 13 percent of controls (i.e., 340 controls) used multivitamin supplements periconceptionally. The multivitamin supplements used were defined as preparations containing "at least two vitamins, one of which was water-soluble" (see Table 2 for definition of supplements). The authors reported an approximate 40 percent reduction in prevalence of NTD's associated with use of supplements. The most common dose of folic acid in the supplements was 0.4 mg (400 µg). For nonusers of supplements, there was a statistically significant trend of decreasing risk of occurrence of NTD's associated with dietary folate intakes of 0.25 mg (250 µg, or 62 percent of the RDI)/day and higher (Table 3). Reductions in risk associated with dietary folate intakes alone were 30 to 40 percent.

PHS, in issuing its September 1992 recommendation (Ref. 11), examined the available human studies discussed above (except the Werler et al. (Ref. 26) study which was not yet publicly available) and concluded:

> In summary, the data available indicate that folic acid can help avert NTDs (neural tube defects) when given at high-dose levels (i.e., 4.0 mg per day). The results of the British MRC study showed that the addition of other vitamins to 4.0 mg of folic acid confers no extra benefit in averting NTDs. Based on a synthesis of information from several studies, including those which used multivitamins containing folic acid at a daily dose level of ≥0.4 mg, it was inferred that folic acid alone at levels of 0.4 mg per day will reduce the risk of NTDs. The protective effect found in the studies of lower-dose folic acid, measured by the reduction in NTD incidence, ranged from none to substantial.

4. Studies in Animal Model Systems

Studies with animal model systems are one of several lines of investigation that are used to establish causal relationships and to elucidate

mechanisms of actions between deficiencies or excesses of various nutrients and adverse outcomes such as birth defects. The agency reviewed relevant animal studies in its proposed rule (56 FR 60610) and noted that such studies have provided some support for the hypothesis that nutrient deficiencies may be one factor in the complex etiology of NTD's. For example, deficiencies of nutrients such as vitamin B_{12}, vitamin B_6, pantothenic acid, and vitamin E have been reported to cause NTD's in some species (Ref. 19). In its proposed rule and final rule, the agency reviewed studies that demonstrated that:

(1) In rats and mice, folate deficiency alone does not produce NTD-affected embryos in a reproducible manner (Refs. 27 and 28), but that rats fed folate-deficient diets in conjunction with antifolate drugs during pregnancy produce embryos with multiple congenital abnormalities (Ref. 29);

(2) Excess vitamin A administered in early pregnancy increases the incidence of NTD's in a mouse model system, and that compounds such as folic acid, folinic acid, vitamin B_{12}, and vitamin E do not significantly affect the incidence of this defect (Ref. 30);

(3) NTD's in the golden hamster model system can be induced by maternal hyperthermia or ethanol following exposures in early gestation, and that folate supplementation begun before such treatments does not prevent the alcohol- or heat-induced defects (Ref. 31); and

(4) There are conflicting reports regarding whether the anticonvulsant drug valproic acid, suspected of causing NTD's in humans, does so through effects on folate metabolism (see 56 FR 60610 and 58 FR 2606 for review).

Overall, these animal studies do not provide evidence for a consistent association between folate nutriture and NTD's, although they do show that disturbed folate metabolism may be one factor in the complex etiology of these defects.

5. Related Data

a. *Maternal vitamin status.* Women with a personal history of an NTD pregnancy have generally been the subject of studies to try to relate maternal nutritional status to pregnancies affected by NTD's. Measurement of maternal or fetal blood levels of specific vitamins is one method used to test the hypothesis that folate status is directly related to risk of an NTD pregnancy. In its proposal (56 FR 60610) and final rule (58 FR 2606), FDA reviewed studies in which levels of various vitamins were measured in the blood of women during or following the periconceptional interval to determine whether maternal vitamin status is related to risk of an NTD-affected pregnancy (Refs. 32, 33, 34, and 35). These studies and studies that became available after publication of the final rule are summarized below.

Yates et al. (Ref. 34), in a study on Scottish women, reported that red blood cell folate levels were significantly lower in women who had two or more NTD pregnancies than in control women. No differences were found in serum folate, vitamin B_{12}, or other serum vitamin measurements (plasma or white blood cell vitamin C, vitamin A, thiamin, riboflavin, vitamin B_6, vitamin E) between cases and controls. The authors reported that dietary intakes of folate among the groups of mothers who had NTD-affected pregnancies and those who did not were not significantly different, and dietary folate intakes did not correlate with pregnancy outcome (Ref. 34).

In another study, Mills et al. (Ref. 35) measured levels of folate, vitamin B_{12}, and vitamin A in maternal serum samples drawn early in pregnancies resulting in offspring with NTD's and in control pregnancies. The results of this population-based study in Finland, a low prevalence area for NTD's, showed no relationship between maternal serum folate, vitamin B_{12}, and vitamin A during pregnancy and risk of NTD's.

In a study published after publication of FDA's final rule, Mooij et al. (Ref. 36) investigated whether periconceptional clinical profiles of vitamin status in women in the Netherlands could provide a means of identifying women at risk of recurrence of an NTD pregnancy. Mooij et al. (Ref. 36) evaluated vitamin status in women who had a history of an NTD pregnancy and who planned a further pregnancy. Participants in the nonrandomized study were volunteers.

Vitamin supplements (one multivitamin plus 5 mg (5,000 µg) of folic acid daily) were offered to 50 women. Eighteen (18) other women were willing to participate in the study but did not want to use supplements. Supplementation began at least 28 days before conception and continued until week 12 of gestation. Vitamin levels were measured in serum or red blood cells preconceptionally and at weeks 6 and 9 of gestation. Six of the 50 vitamin-supplemented women were subsequently excluded because of inadequate data collection. A total of 62 pregnancies were evaluated.

A comparison of preconceptional mean serum or red blood cell vitamin concentrations between the two groups revealed no significant differences for any of the vitamins measured (Ref. 36). During early pregnancy, serum levels of vitamin C and vitamin B_{12} decreased significantly in unsupplemented women but not in the vitamin-supplemented women. Serum and red blood cell folates did not decrease significantly during early pregnancy in unsupplemented women, while significant increases in serum and red blood cell folate occurred in early pregnancy in vitamin-supplemented women. The authors concluded that evaluation of vitamin profiles is not a suitable means of identifying women at risk for NTD's before pregnancy (Ref. 36).

Thus, clinical studies that measured maternal folate status provide no consistent evidence for an association between folate nutritional status and NTD's.

b. *Potential role of nutrients other than folate in etiology of NTD's.* It is well recognized that NTD's may be caused by a number of environmental agents and genetic factors. Nutritional factors other than folate are hypothesized to be involved in causing some human NTD's (see 56 FR 60610 for references). For example, animal studies have shown that deficiencies of some vitamins during pregnancy (such as vitamin B_{12}, vitamin B_6, and pantothenic acid) produce a variety of fetal abnormalities, including NTD's. Several studies showed that decreases in maternal serum levels of vitamin C and vitamin B_{12} were associated with pregnancies complicated by NTD's (Refs. 32, 36, 37, and 38). Epidemiologic studies of NTD's in humans suggest a link with nutrition because of variations in prevalence of such defects with social class, dietary habits, and season (see 56 FR 60610 for references).

Several biological mechanisms have been suggested to explain the causes of NTD's or to explain the roles of putative protective agents. In addition to studies and possible causes already discussed, several other studies have attempted to elucidate additional mechanisms for these defects.

i. *Genetic defects.* It has been postulated that a genetic defect may contribute to some NTD's both in animal model systems and in humans. For example, the disorder homocystinuria (excessively high urinary levels of homocystine, a metabolic product of the essential amino acid, methionine, and an intermediate in the synthesis of the amino acid cystine) is an inherited disorder of the metabolism of methionine. The disorder is caused by a deficiency of an enzyme known as

cystathionine B-synthetase that requires vitamin B_6 for its activity. Folate as well as vitamins C, B_6, and B_{12} are believed to influence the complex metabolism of the amino acid methionine. All of these vitamins must be present in adequate amounts for normal functioning of these complex metabolic pathways.

Steegers-Theunissen et al., (Ref. 39) have performed studies that looked at whether a genetic error in the metabolism of homocysteine and the several vitamins required for homocysteine metabolism may be a risk factor for having a child with an NTD. These authors measured the levels of relevant vitamins and homocysteine during oral methionine loading tests given to 16 women who had given birth to an infant with an NTD and to 15 control women. These authors reported that 5 of 16 women who had an infant with an NTD had clinically demonstrable methionine intolerance in the absence of liver and kidney dysfunction and postulated that an inborn error of homocysteine metabolism may be a risk factor for an NTD-complicated pregnancy (Ref. 39). These authors suggested that an accumulation of plasma homocysteine which arises as a result of the genetic defect may be toxic for the developing embryo. Supplementation with high doses of vitamin B_6 and folate may lower the high blood levels of homocysteine. Steegers-Theunissen et al. (Ref. 39) noted that there was a high incidence of heterozygosity (a heterozygote is a person who carries one gene for a metabolic disorder but who lacks the second gene necessary for the metabolic disorder to be fully expressed) for homocystinuria among the women whose infants had NTD's (31 percent) as compared with the incidence of about 1 percent in the normal population.

ii. *Vitamin B_{12} deficiency.* A possible role for vitamin B_{12} has also been suggested. Recently, Adams et al. (Ref. 41) reported the results of a case-control study of midtrimester sera from 33 NTD cases and 132 control cases from two maternal serum alpha-fetoprotein prenatal screening programs in the United States. Adams et al. (Ref. 41) measured serum levels of methylmalonic acid (elevated levels are an indicator of vitamin B_{12} deficiency (Ref. 40). Adams et al. (Ref. 41) found a highly significant difference in serum methymalonic acid between cases and controls. Mothers with serum methylmalonic acid concentrations greater than the 75th percentile were at significantly increased risk of carrying an NTD-affected pregnancy. These findings may suggest a role for vitamin B_{12} in NTD's.

iii. *Pantothenic acid deficiency.* A possible role for pantothenic acid has also been suggested. In a recent letter to the editor of the *New England Journal of Medicine,* Thurston and Hauhart (Ref. 42) noted that the multivitamin and multimineral preparation used in the recently completed Hungarian trial (Ref. 24) contained pantothenic acid. These authors discussed mechanistic considerations regarding metabolic functions of pantothenic acid and possible interactions between pantothenic acid and valproic acid, an antiepileptic drug whose use in the first trimester of pregnancy increases the risk of NTD's to about 30 times over that in the general population. They also noted that the birth defect exencephaly (exencephaly is considered a defect in rodents that is analogous to NTD's in humans) is characteristic of fetuses of rats that are pantothenic acid-deficient (Ref. 19). They proposed that provision of pantothenic acid might have additional protective effects against NTD's (Ref. 42).

In responding to Thurston's and Hauhart's comments, the authors of the Hungarian trial (Ref. 43) noted:

> We cannot be sure that the preventive effect [of the multivitamin and multimineral supplement] was due to folic acid alone or in association with the other components of the multivitamin. Folic acid, vitamin B_6, vitamin B_{12}, vitamin C, and zinc interact with one another in many metabolic pathways; thus, folic acid may have a synergistic effect with other vitamins. It is also possible that pantothenic acid (vitamin B_5) has some protective effect against neural tube defects.

c. *Role of other factors (maternal health, environmental factors).* A wide variety of factors have been postulated as contributing to the etiology of NTD's (see 56 FR 60610 and 58 FR 2606 for references). Several areas of increased prevalence of NTD's have been described recently, one along the U.S.-Mexico border in Texas (Ref. 44) and another in northern New Jersey (Refs. 21 and 22). A high prevalence of NTD's has also been reported in South Carolina (Ref. 13). Several studies have been conducted to identify factors that may contribute to elevated risk of NTD's in these areas. Information related to such occurrences in two of these areas is summarized below.

i. *Maternal health.* In early 1991, an apparent cluster of NTD (primarily anencephaly) births occurred in Brownsville, Texas (Ref. 44). The Texas Department of Health began a comprehensive investigation and completed a case-control study of 28 cases with dates of conception from January 1, 1989 through January 31, 1991, and 26 normal control births matched by estimated date of confinement. An extensive questionnaire focusing on nutritional, occupational, medical, and environmental factors was also administered to case and control mothers.

Various medical history characteristics were analyzed in this study. Ninety-seven percent of the women who had NTD births reported health problems prior to pregnancy. Twenty-five percent reported febrile illness, and 43 percent reported use of prescribed medications. Corresponding percentages for the control group were: Health problems prior to pregnancy, 0 percent; febrile illness, 12 percent; and use of prescribed medications, 26 percent. Mothers who reported taking any medication (except prenatal vitamins) during pregnancy had a significantly increased risk of pregnancies with NTD's than did mothers who did not use medications during pregnancy (Ref. 44).

The report noted that there were no statistically significant differences in distributions of red blood cell folates between cases and controls. However, six red cell folate values reported as low (less than 140 nanogram/milliliter red blood cells, considered indicative of folate deficiency) were all found in the control group (Ref. 44).

ii. *Environmental exposures.* Several studies have suggested associations between maternal exposure to organic compounds at the workplace or at the home in increased rates of birth defects of the central nervous system (Refs. 21 and 22).

In November 1992, the New Jersey Department of Health reported the results of studies that examined births in New Jersey between 1985 and 1988 (Refs. 21 and 22). The project focused on the development and application of methodology appropriate to assess the relationship between exposure to environmental pollutants and adverse reproductive outcomes. The New Jersey Department of Health utilized its population-based birth defects registry and its vital records, as well as data obtained from the New Jersey Department of Environmental Protection, to evaluate the relationship between residing in an area served by a water supply subsequently reported to be contaminated with organic compounds and adverse reproductive outcomes. Exposures to the contaminants were based on place of residence.

The study analyzed 82,825 total births in the study area between 1985 and

1988. Ninety-eight percent (i.e., 81,055) were singleton (single) births. Congenital anomalies were reported in approximately one (1) percent of all live births (i.e., 791 births). Among births with congenital anomalies, the most frequent adverse outcomes involved cardiac defects (0.46 percent of all live births (370 cases)). Central nervous system defects, including the subset NTD's, numbered 121 (0.15 percent) and 57 (0.07 percent), respectively, of all live births. The rate of NTD's tube defects reported (i.e., 0.07 percent) is about the current prevalence in the U.S. population (i.e., about 0.06 percent; about 6/10,000 live births).

Analyses conducted in the final phase of the project focused on four counties in northern New Jersey (Refs. 21 and 22). The study population included all singleton births and fetal deaths occurring during 1985 through 1988 to mothers residing in one of 75 study towns at the time of birth or fetal death. The contaminants in drinking water of primary interest included total trihalomethanes (TTHM) and the total concentrations of 14 volatile organics tested by New Jersey's Department of Environmental Protection and Energy's A–280 program. Other specific volatile organics were also analyzed in drinking water supplies. Analyses included data from an individual-based cross-sectional study utilizing vital records data for the entire study population without interviews. A second individual-based study utilized a case-control design to sample the study population and to collect more detailed information on each subject through interviews with mothers of the subjects.

Risk of NTD's was found to be increased more than 3-fold in women in residential areas with water supplies containing TTHM at levels greater than 80 parts per billion (ppb) compared with those served by water supplies containing TTHM at the lowest measured concentrations of less than 20 ppb.

C. Federal Government Statements and Other Authoritative Reviews

1. Background

Both in the proposal (56 FR 60610) and in the final rule (58 FR 2606), FDA reviewed Federal government documents including the Surgeon General's Report on Nutrition and Health (Ref. 45), the USDA/DHHS "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 46), the NAS' "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 47), and other authoritative statements related to the topic of folic acid and NTD's. In addition, the agency reviewed statements from professional organizations and recommendations from other countries. These reports and statements, which were published before the results of the MRC trial (Ref. 4), the Hungarian trial (Ref. 24), and the Boston case-control study (Ref. 26) became available, 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 NTD's among women in the general U.S. population.

Following the passage of the 1990 amendments, the agency contracted with the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (LSRO/FASEB; Contract No. 233–88–2124, Task Order No. 9) to independently evaluate the scientific literature respecting folic acid and NTD's (Ref. 48). 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 bearing infants with neural tube defects." The agency noted in its final rule (58 FR 2606 at 2610 January 6, 1993) that, although the final LSRO report (Ref. 49) did not address several issues specifically relevant to health claims questions, there were significant areas in which the agency's proposed rule and the LSRO report were in agreement. These included:

(1) Four mg of folic acid has been demonstrated to have a protective effect against recurrence of NTD's in women at high risk of this complication;

(2) There is no evidence that the effect of folic acid is long-lasting as a protectant or potential protectant against NTD's;

(3) In addition to maternal and fetal nutrition, other individual, dietary, nutrition, and health factors also contribute to risk of NTD's;

(4) There are significant gaps in our knowledge of the etiology of NTD's and of how folic acid, either alone or in conjunction with other vitamins, may protect against NTD's; and

(5) It is currently unknown whether NTD's are caused by a gene-induced or drug-induced dependency requiring a higher than physiologic intake of folate or other micronutrient (58 FR 2606).

In 1992, the Institute of Medicine (IOM) of NAS updated its report *Nutrition During Pregnancy* (Ref. 50) to reflect new data (primarily the results of the MRC trial; Ref. 4) that had become available since the first publication of the report. Data from the Hungarian randomized intervention trial (Ref. 24) and the Boston case-control study (Ref. 26) were not publicly available at the time the report was updated. The IOM report noted that a previous history of an NTD should alert health care providers to the need for preventive measures before a subsequent pregnancy. The report recommended that women with a history of an NTD-complicated pregnancy follow the CDC recommendations (Refs. 51 and 52) for high-dose folic acid supplementation (preconceptionally and throughout the first trimester, under a physician's supervision) to reduce their risk of recurrent NTD's (Refs. 51 and 52). The report noted that questions remain concerning the etiology of NTD's, the most appropriate dosage of folic acid, and the appropriate role of nutrition in preventing first occurrences.

2. Recent Statements of Federal Agencies and Professional Organizations

a. *Health Resources and Services Administration.* In May, 1993, the Maternal and Child Health Bureau of the Health Resources and Services Administration, DHHS, (Ref. 17), as part of its responsibility to provide education to health professionals, prepared a fact sheet on folic acid and NTD's for physicians and other health care providers. This fact sheet provides specific nutrition education information to health care providers as a method of implementing the PHS recommendation and provides specific examples of dietary plans that provide over 0.4 mg of folate/day for women with energy needs and caloric intake lower than 2,200 calories. The report notes that women who cannot be assured of adequate dietary folate intake should be informed of the option of using a folate supplement. The report notes that even if the PHS recommendation is followed, about 50 percent of NTD cases will continue to occur in spite of increased folate intake, and that periconceptional folate intake does not negate the need to offer prenatal screening for maternal alpha-fetoprotein and other markers. Noting that the safe range of folate intake is unclear, the report stated that high doses of folate present certain potential problems including masking of pernicious anemia and risks to persons undergoing therapy with medications that interfere with folate metabolism (Ref. 17).

b. *The Committee on Obstetrics (Maternal and Fetal Medicine) of the American College of Obstetricians and Gynecologists (ACOG).* The ACOG recently published its opinion regarding the use of folic acid to reduce the risk of recurrent NTD's and possible

reduction in risk of first occurrences of NTD's (Ref. 20). The ACOG report identified women at increased risk for a first occurrence as those with a close relative (e.g., sibling, niece, nephew) with an NTD; with insulin-dependent diabetes mellitus; or with seizure disorders who are being treated with valproic acid or carbamazepine. The ACOG report (Ref. 20) noted that the efficacy of folic acid supplementation has not been evaluated in these patients, whose risk for an occurrence of an NTD is 0.3 to 1.0 percent, compared to a risk of about 0.06 percent in women without these characteristics.

The ACOG report noted that because of difficulties associated with taking daily supplements throughout the childbearing years and because of variations in the amount and availability of folate in foods, it is not clear how the PHS recommendation that all women of childbearing age who are capable of becoming pregnant should consume 0.4 mg folic acid/day throughout their childbearing years can be accomplished. With respect to fortification of food with folic acid, the report noted that this strategy will require careful consideration of the risk-benefit ratio for the entire population, including those with vitamin B_{12} deficiency.

The ACOG report noted that to date no prospective randomized controlled trials on the use of folic acid supplementation to prevent NTD's in the United States have been reported, and that without such trials, the potential benefit in the U.S. population can be estimated only indirectly. The ACOG report stated that because the benefit of folic acid in reducing the risk of first occurrences of NTD's defects has not been established by prospective randomized trials, obstetricians should continue to offer screening for elevated serum alpha-fetoprotein to pregnant women, including those who consume 0.4 mg of folic acid daily.

c. *The American College of Rheumatology.* The American College of Rheumatology, in a statement regarding use of folic acid in conjunction with the antifolate medication Methotrexate in patients with arthritis, stated that consumption of folic acid at a dose of 1 mg/day does not appear to inhibit the efficacy of low-dose weekly Methotrexate therapy in rheumatoid arthritis, and that the PHS recommendation for women of childbearing age to consume 0.4 mg of folic acid/day should have no impact on the efficacy of low dose weekly Methotrexate regimens (Ref. 53).

3. Recommendations in Other Countries

a. *The Netherlands.* The Netherlands Food and Nutrition Council (the council), in its "Report on the Relationship Between Folic Acid Intake and Neural Tube Defects" (Ref. 54), concluded that research results do not justify recommendations to stimulate the use of folic acid supplements or multivitamin supplements as a method of primary prevention of NTD's. The report noted that no studies have been carried out on the link between folic acid intake, the folic acid status of the mother, and the occurrence of NTD's, and that it is vital to know whether maternal folic acid status or folic acid intake in the periconceptional period constitutes a risk indicator for the occurrence of NTD's. The Council's report recommends that women of childbearing age eat diets that provide 200 to 300 µg (0.2 to 0.3 mg) of folic acid/day.

b. *The United Kingdom.* The United Kingdom Guidelines to physicians, nursing officers, and directors of public health (Ref. 55) recommend that women likely to become pregnant increase their intakes of folate/folic acid by eating more folate-rich foods, not over-cooked, and by eating foods fortified with folic acid. It also recommends that women planning a pregnancy should consume a 0.4 mg folic acid supplement daily from the start of trying to conceive until the twelfth week of pregnancy.

The guidelines further recommend that an increased range of folic acid-fortified breads and cereals should be made available and recommended fortification levels for specified foods as follows: Soft grain bread, 105 µg folic acid/serving (typical serving size=2 slices); cornflakes or branflakes, 100 µg folic acid/serving.

c. *Canada.* The Health Protection Branch, Health and Welfare Canada (Ref. 56) has recommended that:

(1) As early as possible when planning a pregnancy, women should consult their physicians about folic acid supplements;

(2) Women who have had a previous pregnancy with an NTD are at a high risk of recurrence and should consult their physician about folic acid supplements; and

(3) All women of childbearing potential should follow Canada's *Food Guide to Healthy Eating* and take care to choose more foods that are high in folate.

With respect to supplement use, Health and Welfare Canada recommends that women consult their physicians before deciding on taking a folic acid supplement. They note that a high intake of folic acid (greater than 1 mg/day) may complicate the diagnosis of vitamin B_{12} deficiency, and that although vitamin B_{12} deficiency is rare in reproductive-age women, irreversible neurologic damage may occur if vitamin B_{12} deficiency is not diagnosed and properly treated. The report also notes that folic acid may have an adverse effect on the drug control of epilepsy. Women taking anticonvulsants and those taking folic acid antagonists such as Methotrexate should be individually counselled by their physician regarding folic acid supplementation.

In addition, Health and Welfare Canada was concerned about increased use of multivitamins to obtain folic acid. The report noted that multivitamins usually contain vitamin A, and that too much vitamin A can harm a developing fetus or have toxic effects on an individual. For these reasons, the recommendation stated that the daily dosage recommended on the multivitamin label should be followed.

D. Summary of FDA's Discussions With the Folic Acid Subcommittee

1. Background

As explained above, in October 1992, FDA empaneled the Folic Acid Subcommittee to help resolve the outstanding issues identified in the PHS recommendation. The Folic Acid Subcommittee members were drawn primarily from existing FDA advisory committees, including the Food Advisory Committee, and included individuals with expertise in the fields of food composition, epidemiology, human nutrition, folate metabolism, geriatrics, food fortification, rheumatology, women's health, consumer interests, oncologic drugs, pediatrics, and hematology.

2. Folic Acid Subcommittee Meeting, November 23 and 24, 1992

The first meeting of the Folic Acid Subcommittee was held on November 23 and 24, 1992 (57 FR 52781; Refs. 12 and 57). Areas of expertise represented by consultants invited to speak to the Folic Acid Subcommittee at its first meeting on November 23 and 24, 1992 included NTD's, epidemiology, folate metabolism, special populations, bioavailability of folates, pernicious anemia and vitamin B_{12}-related problems, convulsive disorders, food fortification, folate as a drug, and Federal food programs such as school lunch programs and the Women, Infants, and Children (WIC) program.

At the open meeting held November 23 and 24, 1992, the Folic Acid Subcommittee heard testimony from

expert speakers and others on the daily intake of folate adequate for reduction in risk of NTD's, safety concerns for persons in the target population and in the general population, and the appropriateness of a health claim on the labels or labeling of foods (Ref. 12).

a. *Issues.* The Folic Acid Subcommittee's discussion of the target population and of the appropriate daily folate intake focused on questions of the appropriate level of folate in food to attain the claimed effect and yet to ensure safety; the importance of timing of intervention because the neural tube closes early in pregnancy, often before a woman realizes that she is pregnant; the adequacy of the evidence relating folate nutritional status itself to risk of NTD's; and safety concerns relative to the potential for increased folate intake to mask the hematologic manifestations of vitamin B_{12} deficiency and thus to delay diagnosis and treatment of this deficiency while irreversible neurologic damage progresses.

With respect to identifying women in the target population who may be at particular risk of occurrence of an NTD-affected pregnancy, the Folic Acid Subcommittee acknowledged that it was not possible to identify such women. There was agreement that because many pregnancies are unplanned, and because the neural tube forms and closes very early in gestation, the recommendation for adequate intake of folate should be directed at all women throughout their childbearing years. Expert speakers noted the inherent difficulties in reaching the entire target population of women of childbearing age with educational programs alone and in motivating them to change eating practices. The speakers discussed the advantages of food fortification in reaching the greatest number of the target population without requiring conscious changes in food selection practices. The expert speakers and the members of the Folic Acid Subcommittee also considered issues of effectiveness of dietary intake and of doses of folate lower than the recommended 0.4 mg (400 µg) in reducing risk of NTD's. They discussed results of several studies suggesting protective effects against NTD's of dietary folate intakes lower than 0.4 mg (400 µg)/day (i.e. at levels of 0.25 mg or more daily).

In considering the available data regarding folic acid and NTD's, some members of the Folic Acid Subcommittee raised questions as to whether the available data were sufficiently sound or generalizable to the U.S. population to warrant a conclusion that fortification of the entire food supply or universal supplement use would reduce the risk of occurrence of NTD's in women in the U.S. population. They noted that since a fortification strategy would affect 250 to 260 million people, the data on which the need for such a proposed intervention is based should be examined critically. Other members, although noting uncertainties in the data, found the data sufficiently convincing to recommend some types of public health action to implement these findings for U.S. women.

With respect to safety considerations raised by the possible fortification of the food supply, the greatest concern was for persons at risk of vitamin B_{12} deficiency. The population groups for which there was most safety concern because of relatively high prevalences of low serum vitamin B_{12} levels, were the elderly, young African-American women, and acquired immunodeficiency syndrome (AIDS) patients. Additional safety questions included consideration of persons taking antiepileptic medications and those prescribed antifolate medications for a wide range of disorders.

In considering how to ensure that women have an adequate folate intake, the Folic Acid Subcommittee discussed the possibility of educating women of childbearing age on improving their dietary habits, use of supplements throughout a woman's childbearing years, and fortification of the food supply with folic acid to achieve the recommended intake. The majority of the members of the Folic Acid Subcommittee and many of the invited expert consultants expressed concern about the current lack of monitoring and surveillance for potential adverse effects of increased folate intake.

b. *Recommendations.* At the close of its November 23 and 24, 1992, meeting, the Folic Acid Subcommittee provided several recommendations. Those relevant to the health claim issue were:

i. *Health claims.* The Folic Acid Subcommittee members supported the PHS policy regarding folic acid and NTD's. The Subcommittee, however, recommended against a health claim on food labels or labeling because the majority of the Subcommittee members expressed concern that the data on the specific relationship between folate, at levels attainable from usual diets, and NTD's were not strong enough to support a food label health claim on this relationship.

ii. *Educational activities.* The Folic Acid Subcommittee recommended that PHS and FDA develop and implement an educational program, directed at women of childbearing age, emphasizing the importance of sound dietary choices to achieve nutrient intakes provided in dietary guidelines. The Folic Acid Subcommittee also stated that the PHS should work with health professionals and others to develop and implement educational efforts that emphasize the importance of diets that meet established dietary guidelines, the importance of maintaining intake of folate sufficient to reduce the risk of NTD's, and the importance of detection, diagnosis, and treatment for persons with low vitamin B_{12} status.

c. *Comments.* Following the November 23 and 24, 1992, meeting of the Folic Acid Subcommittee, the agency received letters from several experts who were invited to speak at the subcommittee meeting. One expert noted that the National Research Council (NRC) in 1989 identified 0.4 mg (400 µg) folic acid as RDA for pregnant women and urged the agency to adopt 0.4 mg (400 µg) folic acid as the RDA for all women capable of becoming pregnant. The agency notes that it is currently using the value of 800 µg (0.8 mg)/day as the RDI for pregnant women and 400 µg (0.4 mg)/day as the RDI for the general population, including women of childbearing age, in accord with the requirements of § 101.9 (21 CFR 101.9) as amended in the **Federal Register** of January 6, 1993, and the requirements of the DS Act of 1992 that FDA not change the U.S. Recommended Daily Allowance levels for nutrients until at least November 8, 1993.

One expert stated that health claims should not be allowed for folic acid-fortified foods or folic acid-containing supplements unless such claims were balanced by a statement that use of such products may increase the frequency of irreversible neurologic damage from vitamin B_{12} deficiency, and that among Black and Hispanic females, folic acid fortification or supplementation is likely to do more harm than good. The agency notes that its proposed requirements for a health claim for folate and NTD's include a requirement that fortified products containing more than 100 µg folic acid per serving carry a statement warning against intake above 1 mg/day (proposed § 101.79(c)(2)(i)(G)).

Several experts expressed concerns about the potential risks of excess folate intakes, particularly in persons over 50 years of age, or of prolonged exposure. These comments also expressed concern that adequate surveillance systems to detect adverse effects of whatever policy is implemented with respect to folic acid were needed. They also noted that no adequate surveillance system for potential masking of vitamin B_{12}

deficiency exists at this time, and that a real commitment should be made to this task.

The agency notes that issues related to establishing surveillance systems for adverse effects of increased folate intakes, particularly with respect to vitamin B_{12}-related problems, were discussed at a public meeting held at the Centers for Disease Control on August 12, 1993 (58 FR 40149 and Ref. 58). The experts agreed that establishment of surveillance systems for masking the anemia of vitamin B_{12} deficiency would be extremely difficult, but CDC indicated a commitment to this task. FDA also notes that it has a long-standing history of collaborating with the National Center for Health Statistics (NCHS) of CDC to use nutritional assessment data from their National Health and Nutrition Examination Surveys (NHANES) to monitor the nutritional status of the U.S. population. FDA intends to continue this collaboration, particularly as it relates to folate and vitamin B_{12}.

Several experts stated that, with respect to reduction in risk of NTD's, the 400 µg (0.4 mg) dose of folic acid is an artificial goal and cited studies (Refs. 6, 8, 9, and 26) that show strong protective effects of dietary folate intakes at levels greater than 100 µg/day.

The agency recognizes the importance of the dietary studies that have shown protective effects against occurrence or recurrence of NTD's at intakes of folate lower than 0.4 mg (400 µg) and has summarized the findings of these studies in Table 3. The agency agrees that consumption of diets providing adequate amounts of folate is important and notes that it used the findings of studies that showed a benefit from diet in its development of the model health claims included in this proposal.

Another comment included a recommendation for a modification of the method used by the agency in estimating daily folate intakes by individuals. Specifically, the comment suggested that the within-individual component of variance resulting from use of the mean of 3 days of daily intake be removed, and that the intake distributions be recalculated using only the between-individual component of variance.

The agency did not use this suggested modification in its analyses because FDA believes that systematic bias is a more serious problem than random error, and that use of sophisticated mathematical corrections would attribute a degree of precision to the food intakes values that is not justified.

3. Folic Acid Subcommittee Meeting, April 15, 1993

a. *General description.* FDA reconvened the Folic Acid Subcommittee on April 15, 1993 (58 FR 15149, March 19, 1993; Refs. 13 and 58). The purpose of this meeting was to obtain comments on the options that FDA had developed on possible ways to increase the folate intake of women of childbearing age. These options included fortification of specific products, such as cereal-grains, at levels of 70, 140, or 350 µg folic acid/100 g and use of food labeling to provide information to consumers (e.g., health claims and content and descriptive labeling that would serve to identify "good sources" and "excellent sources" of dietary folate). The agency noted that, with respect to health claims, at the November 23 and 24, 1992, meeting, the majority of Folic Acid Subcommittee members did not believe that the data on a specific relationship between folic acid, at levels attainable from usual diets, and NTD's was strong enough to support a claim. The agency, among other things, asked for clarification of the opinions of the Folic Acid Subcommittee members on this issue.

b. *Health claims.* As stated above, FDA pointed out that there was an apparent inconsistency in the Folic Acid Subcommittee's recommendations regarding health claims in that the majority of Folic Acid Subcommittee members did not believe that the scientific data on a specific relationship between folate, at levels attainable from usual diets, and NTD's were strong enough to support a food label health claim for this relationship. On the other hand, the Subcommittee supported the PHS recommendation that women of childbearing age should consume 0.4 mg of folate/day to reduce the risk of an NTD pregnancy, which, if it were to appear on a food label, would constitute a health claim as defined by the 1990 amendments.

The agency asked the Folic Acid Subcommittee whether it would still recommend against authorizing a health claim, and whether such a claim, if authorized, could provide useful information at point of purchase in helping consumers understand the relationship between folate and risk of NTD's within a total diet without being misleading or raising undue safety concerns. The agency also asked the Folic Acid Subcommittee for its views on specific elements that might be included in a health claim.

Extensive discussion by the Folic Acid Subcommittee of this matter revealed a shift in views, with five of the nine Folic Acid Subcommittee members favoring, and four of nine opposing, a food label health claim on the relationship between folate and NTD's. Those favoring a health claim cited its potential educational value. One member favored a health claim only as part of a general educational effort directed both at women of childbearing age and at members of the general population who may be at risk of adverse effects from increased intakes of folate. Another member favoring a carefully worded health claim cited its potential to encourage increased consumption of folate while simultaneously providing a label warning regarding excess intakes.

Those opposing a health claim cited the weakness of the data supporting the nutrient-disease relationship, including the very small number and the observational nature of studies relating intake of folate at levels attainable from usual diets to reduced risk of NTD's. Other members opposing a health claim expressed concern that strong marketing efforts for health claim-labeled foods could cloak the weakness of the science base for the claim, and that such efforts could be potentially misleading to many women who might be led to believe that they could avoid all birth defects through use of folate.

4. Summary Presented to the Food Advisory Committee

The results of the Folic Acid Subcommittee's meeting were summarized for FDA's Food Advisory Committee on April 16, 1993 by the Chairman of the Folic Acid Subcommittee. Additional views were presented to the Committee by several Folic Acid Subcommittee members. The Food Advisory Committee Chairman noted that although the **Federal Register** notice announcing the Folic Acid Subcommittee meeting on April 15, 1993 (58 FR 15149) had stated that the parent Food Advisory Committee would take action on the Folic Acid Subcommittee's recommendations on April 16, 1993, no action would be taken because the Subcommittee's activities were still in progress. The Chairman noted the division among the members of the Folic Acid Subcommittee on the issue of whether a health claim should be authorized by FDA.

E. Tentative Decision To Authorize a Health Claim on Labels and in Labeling of Foods in Conventional Form and Dietary Supplements

In its final rule published January 6, 1993 (58 FR 2606), FDA announced its decision not to authorize a health claim

on the relationship between folic acid and NTD's. The agency noted that section 403(r)(3)(B)(i) of the act authorizes the agency to grant a health claim on food other than dietary supplements when there is significant scientific agreement that the scientific data relating a nutrient to a disease or health-related condition support such a claim. The agency noted in its final rule that the PHS recommendation evidenced that such agreement exists.

The agency also noted, however, that sections 402(a), 403(r)(3)(A)(ii), and 409 of the act (21 U.S.C. 348), require that the use of a substance in food that is the subject of a health claim be safe. The PHS recommendation itself (Ref. 11) stated that questions remained about the safety of high intakes of folate by both the target population and other segments of the population who might be unintentionally exposed to high intakes of folic acid if overfortification of the food supply were to occur as a result of the PHS recommendation or efforts to qualify to bear a health claim. The agency also noted that there were several other unresolved scientific questions that required discussion before a health claim could be authorized. Based on the concerns expressed in its final rule, FDA concluded that it could not authorize a health claim on folic acid and NTD's at that time.

In developing this proposal, the agency reviewed all of the publicly available studies on the relationship between folate and NTD's. Based on its own review of the totality of the scientific evidence, FDA has tentatively concluded that the available data show that diets adequate in folate can reduce the risk of NTD's.

The strongest evidence for this relationship comes from the MRC intervention study that showed that women at risk of recurrence of an NTD-affected pregnancy who consumed a supplement containing 4 mg (4,000 µg) folic acid daily had a reduced risk of having a child with NTD's. This study clearly demonstrated, for the first time, a significant reduction in recurrence of NTD's with high levels of folic acid but not with other vitamins or minerals. This study established a specific role for folic acid in reducing the risk of recurrence of neural tube pregnancies in women with a previous history of this defect.

In addition, based on its review of the Hungarian intervention trial that used a multivitamin and multimineral preparation containing 0.8 mg (800 µg) of folic acid, and its review of the five published observational studies that reported use of multivitamins containing 0 to 1,000 µg of folic acid, the agency has tentatively concluded that most of these studies had results consistent with the conclusion that folate, at levels attainable in usual diets, may reduce the risk of occurrence of NTD's.

Although most of the available studies used dietary supplements containing approximately 400 µg or more of folic acid daily, several studies also showed a beneficial effect of dietary intakes of 250 µg or more daily, a level consistent with the estimated folate intake necessary to saturate body stores of folate (Ref. 12).

In reaching this tentative conclusion, FDA acknowledges that there are significant gaps in existing knowledge about the etiology of NTD's; about how folate, either alone or in combination with other nutrients, reduces the risk of NTD's; and of the dose-response relationship of folate intake to reduction in risk of NTD-affected pregnancies. However, even with these uncertainties, PHS, in examining the data from the available human studies, found the evidence sufficiently consistent to develop its recommendation that all women capable of becoming pregnant should consume 400 µg folic acid daily. FDA supported this decision at the time it was made (Ref. 11) and in its final rule (58 FR 2606). Additional support was expressed by FDA's Folic Acid Subcommittee. Thus, the agency has tentatively concluded that, as evidenced by the PHS recommendation and the agency's discussions with the Folic Acid Subcommittee (Ref. 12), there is significant scientific agreement on the relationship between folate and a reduction in the risk of NTD's.

The agency has also extensively reviewed safety issues identified in its proposed and final rules and discussed these issues with the Folic Acid Subcommittee (Ref. 12). Based on its review of the scientific evidence, its discussions with the Folic Acid Subcommittee, and the comments it has received, the agency has tentatively concluded that safety problems can be resolved by setting a safe upper limit of intake of 1 mg of folate/day for all population groups. Thus, the agency has tentatively concluded that a health claim on the topic of folate and NTD's will not increase risk to persons in the general population or in the target population of a disease or health-related condition when daily intakes of folate are limited to 1 mg. FDA tentatively concludes that daily folate intakes can be maintained within safe limits by allocation of folic acid to specific foods in the food supply through an amendment to the food additive regulation for folic acid.

Therefore, in this document, the agency is proposing to authorize a health claim for folate and NTD's on the labels and labeling of foods and on dietary supplements. In companion documents published elsewhere in this **Federal Register**, the agency is proposing to amend the food additive regulation for folic acid and to amend the standards of identity for specific cereal-grain products.

IV. Summary of Proposed Resolution of Safety Concerns

The agency has tentatively concluded, based on its review of the scientific evidence, its discussions with the Folic Acid Subcommittee, and its review of comments that it has received, that there are risks attendant on excessive intakes of folate. The primary concern is for persons with vitamin B_{12}-related conditions, although risks may also be created for pregnant women, persons on antiseizure (i.e., antiepileptic) medications, and those on antifolate medications.

The agency's review of the scientific literature, its discussions with the Folic Acid Subcommittee, and its review of the comments that it received, also show that these safety concerns can be largely resolved by limiting addition of folic acid to food through the agency's authority to regulate the use of food additives. The agency has tentatively concluded that its overriding responsibility in seeking to ensure that there is adequate folate in the food supply is to ensure that even with the fortification of foods that it is proposing to provide for, the amount of folate that people are reasonably expected to consume is within the safe upper limit of consumption. The agency has tentatively concluded that the safe upper limit of daily intake of folate for the general population is 1 mg.

The agency is providing a summary of specific safety issues in this document. Additional references can be found in the agency's proposed rule (56 FR 60610, November 27, 1991), its final rule (58 FR 2606; January 6, 1993), and in the extensive briefing materials provided to participants at the Folic Acid Subcommittee meetings (Refs. 57 and 58).

A. Vitamin B_{12}-Related Issues

1. Review of Available Data

As noted above, in the presence of excess folate and inadequate vitamin B_{12}, the megaloblastic anemia of vitamin B_{12} deficiency may not develop, but severe and irreversible nerve damage

may continue (Ref. 14). This interaction between the functions of folate and vitamin B_{12} has been recognized for many years (Ref. 14). Because the anemia of vitamin B_{12} deficiency is often the first clinical symptom to appear, and one that requires further tests to accurately identify its cause, the activity of folate to "mask" the development of the anemia of vitamin B_{12} deficiency is the basis for the requirement for the precautionary statement on oral and parenteral preparations of folic acid used for treating folate-deficiency anemias.

Following the identification and chemical synthesis of folic acid in 1946, but before the isolation of vitamin B_{12}, folic acid, usually in doses of 5 mg or higher, was used to treat pernicious anemia. A number of studies reported that the anemia in many pernicious anemia patients is correctable, at least temporarily, by administration of folic acid (Refs. 60, 61, 62, 63, 64, and 65). However, a number of other studies showed that, while doses of 5 mg of folic acid daily can reverse the hematologic abnormalities of vitamin B_{12} deficiency (Refs. 66, 67, 68, 69, and 70), neurologic damage progresses. Hall and Watkins (Ref. 66) reported neurological degeneration within 2 to 5 months in 14 patients with vitamin B_{12} deficiency who were treated with oral doses of 5 to 20 mg folic acid. In another study, 55 of 98 patients (56 percent) in a clinical study in which patients with pernicious anemia were treated with 5 mg folic acid orally for up to 3.5 years suffered hematologic relapses, neurologic relapses, or combined system relapses (Ref. 68). Although the neurologic degeneration was not caused by the folic acid treatment, their data clearly demonstrate the potential of folic acid to mask the anemia of vitamin B_{12} deficiency without stopping degenerative results of this deficiency.

The first demonstration of dramatic beneficial effects of vitamin B_{12} in treating pernicious anemia occurred in 1948. The advent of the specific therapy for the pernicious anemia of vitamin B_{12} deficiency during the late 1940's and early 1950's diminished the use of high levels (5 mg or 5,000 µg) of folic acid in patients with this condition. Because 1 mg of folic acid became the more common therapeutic dose for folate deficiency, there are limited data available on the effects of doses of folic acid lower than 5 mg in persons with pernicious anemia.

Despite the lack of systematic evaluation of the effect of folic acid on the anemia of vitamin B_{12} deficiency at intakes less than 5 mg/day, several case reports have described hematologic improvement in pernicious anemia with doses of folic acid lower than 1 mg (e.g., 200 to 500 µg) (Refs. 64, 65, 72, 73, and 74). Chosy et al. (Ref. 73) reported that daily injections of 400 µg (0.4 mg) of folic acid caused hematologic responses in three of five patients with pernicious anemia. Other investigators have reported suboptimal responses to 0.5 mg of folic acid administered intramuscularly or orally to patients with pernicious anemia (Refs. 64 and 65). On the basis of the reticulocyte response, 0.2 mg (200 µg) of folic acid has been used to differentiate between the megaloblastic anemias caused by folate deficiency and vitamin B_{12} deficiency (Ref. 14). Some investigators, however, have not been convinced that amounts of folic acid within the range of 200 to 500 µg/day (0.2–0.5 mg) would mask pernicious anemia (Refs. 72 and 75). Marshall and Jandl (Ref. 72) concluded that from 200 to 500 µg of folic acid daily should suffice for the prevention of folic acid deficiency without endangering patients with undiagnosed pernicious anemia, while larger doses should be reserved for prescription use in patients with abnormal absorption or utilization of folic acid. The results of these studies show, in general, that responses of doses of folic acid below 1 mg have been less predictable than those to doses of 5 mg and higher.

In summary, the available evidence shows that as many as 50 percent or more of patients with pernicious anemia will show a normalization of their anemias with doses of 5 mg of folic acid and higher. Although there are no systematic studies to evaluate the effect of folate on masking the pernicious anemia of vitamin B_{12} deficiency between intakes of 1 and 5 mg daily, several case reports suggest that some patients with pernicious anemia will respond to folate in doses of less than 1 mg/day. Results at these low levels are often suboptimal and less predictable than those occurring at higher intakes.

2. Current Information Regarding Vitamin B_{12} Deficiency in the United States

There is currently no way to determine how many persons in the general U.S. population have undiagnosed vitamin B_{12} deficiency, and thus, how many are potentially at risk of developing pernicious anemia. However, vitamin B_{12} deficiency anemias are not uncommon in the U.S. population. Although not appropriate for determining prevalence, information from NCHS provides some evidence of the potential magnitude of this condition. There were 740,000 patient visits to physicians' offices with a diagnosis of pernicious anemia during the 2-year interval 1989–1990 (Ref. 76). Approximately 524,000 of these visits were by women (Ref. 76). (The number of "visits" recorded in the ambulatory care surveys mentioned above may include multiple visits by some patients and therefore, these data do not represent numbers of patients.) An additional 16,000 patient visits during this interval involved a diagnosis of other vitamin B_{12} deficiencies (for example, those associated with consumption of vegetarian diets). NCHS records from the National Hospital Discharge survey for 1990 identified 31,000 discharges that included a diagnosis of pernicious anemia and an additional 7,000 discharges that included a diagnosis of other vitamin B_{12} deficiency anemias (Ref. 77).

3. Evaluation of Vitamin B_{12} Status

Experts at the November 23 and 24, 1992, Folic Acid Subcommittee meeting noted that there are an unknown but likely significant number of cases of undiagnosed, untreated, and stopped-treatment cases of vitamin B_{12} deficiency in the U.S. population. Evaluation of vitamin B_{12} status is usually not performed during routine clinical examinations. In addition, physicians may not further evaluate low serum vitamin B_{12} levels when such are reported, particularly when anemia and macrocytosis are absent and the serum vitamin B_{12} level is only slightly low (Ref. 81). The diagnosis of vitamin B_{12} deficiency is not always straightforward. For example, Lindenbaum et al. (Ref. 40) reported that while serum vitamin B_{12} levels have been generally considered to be essentially 100 percent sensitive in the detection of clinical disorders caused by vitamin B_{12} deficiency, there are a significant minority of patients with vitamin B_{12} deficiency whose serum vitamin B_{12} levels are normal. In such individuals, measurements of serum metabolite concentrations of methylmalonic acid and total homocysteine may be necessary to facilitate the diagnosis of vitamin B_{12} deficiency (Ref. 40).

In addition to the difficulties with determining vitamin B_{12} status mentioned above, participants in the Folic Acid Subcommittee meetings noted that, despite modern analytical tools available, diagnoses of vitamin B_{12} deficiency can be missed because automated systems are used for routine blood analysis, and direct examination of peripheral blood smears (a laboratory measure that detects red blood cell abnormalities characteristic of various vitamin deficiencies) is not as routine as

was once the case. Often, a number of visits to a physician may be needed, or visits to more than one physician, before an accurate diagnosis of vitamin B_{12} deficiency is made. Additionally, physicians may not recognize that some patients with neuropsychiatric symptoms may have vitamin B_{12} insufficiency.

4. Uncertainties Regarding the Number of Persons Potentially at Risk From High Intakes of Folate

Pernicious anemia is responsible for about 70 percent of vitamin B_{12} deficiency states (Ref. 12). It is recognized that among African-Americans, particularly African-American women, pernicious anemia is not confined to the elderly, as it generally is among Caucasians (Refs. 78, 79, and 80) but occurs at younger ages (e.g., in young African-American women less than 40 years of age). A large number of people have subnormal levels of serum vitamin B_{12} without having any classical manifestations of vitamin B_{12} deficiency (Refs. 82 and 83). Ten to 20 percent of elderly persons, more than 25 percent of demented patients, 15 to 20 percent of AIDS patients, and 15 to 20 percent of patients with malignant diseases have low serum vitamin B_{12} levels. In addition, 5 to 10 percent of all patients, regardless of age or clinical status, are found to have low serum vitamin B_{12} levels. Metabolic and subtle neurologic dysfunction are demonstrable in a significant fraction of such cases (Ref. 82). Very little is known about whether folate supplementation has any effect on such persons with low serum vitamin B_{12} levels (Ref. 82). Participants in both FDA's Folic Acid Subcommittee meetings and the recently convened CDC meeting expressed similar uncertainties regarding potential effects of increased folate intake in the large number of persons with low vitamin B_{12} status (Refs. 12 and 59).

The potential effect of increased folate intakes on nontarget populations with poor or marginal vitamin B_{12} status (including but not limited to pernicious anemia) was the major safety issue discussed by the Folic Acid Subcommittee during the November 23 and 24, 1992 meeting (Ref. 12). Some expert speakers, citing data on the prevalence in the United States of undiagnosed pernicious anemia, expressed concern about masking this condition when high folic acid intakes correct the hematologic effects of a vitamin B_{12} insufficiency, thus delaying diagnosis and treatment while irreversible neurologic damage progresses. Other speakers felt that the safety concerns were overplayed. They noted that diagnoses can be made from the neurologic symptoms and by use of other tools available to physicians. Most expert speakers agreed that physicians and health care professionals need to be trained to be more sensitive to the diagnosis of vitamin B_{12} deficiency.

Some expert speakers and Folic Acid Subcommittee members also noted that there is a lack of recent experience in the United States with individuals taking high doses of folic acid (Ref. 12). Expert consultants to FDA's Folic Acid Subcommittee also pointed out that there is a lack of data from which to estimate the potential risk if folic acid intake is increased in persons with vitamin B_{12}-related problems. Estimates of the size of the population potentially at risk (roughly 13,000 individuals by one estimate and higher by other estimates) were presented by the expert consultants and were discussed by the expert consultants in relation to the potential reduction in the number of NTD-affected pregnancies that might be realized per year by increased folate intakes (estimated at about 1,250 to 2,000). The expert consultants cautioned that the data were inadequate to accurately assess the size of the population potentially at risk.

5. Tentative Conclusion Regarding Safe Upper Limit of Intake for Persons With Vitamin B_{12} Deficiency

Based upon its review of the scientific literature and its discussions with the Folic Acid Subcommittee, FDA has tentatively concluded that safety issues with respect to persons in the population with vitamin B_{12}-related problems can be resolved by setting a safe upper limit of intake of 1 mg of folate/day from all sources for all population groups when considering options for food fortification. This tentative conclusion is based on data that show that, in persons with pernicious anemia, adverse effects have been reported consistently and with high frequencies with daily intakes of 5 mg folic acid and above. Hematologic responses in persons with pernicious anemia have also been reported, although infrequently, at oral or intramuscular exposures below 1.0 mg (see references above). The agency recognizes that once vitamin B_{12} became available in the late 1940's and was used successfully in the treatment of pernicious anemia, treatment of this disease with high doses (5 mg or more) of folic acid diminished, and thus, data on effects of intakes between 1 and 5 mg daily were not generated. Thus, the shape of the intake-response curve for adverse effects of folic acid intakes between 1 and 5 mg is not known. Experts at the recent CDC meeting were asked specifically about this issue, and they stated that, because of the lack of data, it was not possible to state that continuous intakes of 1 mg or more daily by persons with vitamin B_{12} deficiency were safe (Ref. 59).

They noted, additionally, several concerns at intakes above 1 mg daily. One such concern was based on knowledge of the metabolism of folic acid. For example, after an oral dose of 0.5 mg (500 µg) of synthetic folic acid, a small but measurable amount of unmetabolized folic acid appears in the urine (Ref. 16). As intakes increase, substantially larger amounts of the oxidized form of the monoglutamate folate circulate in the blood and are excreted in the urine. The oxidized form of folic acid, normally not found in body tissues to an appreciable degree, passes through the systemic circulation before being excreted, thus exposing body tissues to a form of the vitamin not normally encountered. The effect of long-term continuous exposure to this form of folate has not been evaluated.

In reaching its tentative decision regarding use of a safe upper limit of intake of 1 mg folate/day, FDA recognizes that there are considerable uncertainties in determining the number of persons in the general population who have low vitamin B_{12} status and who may be at particular risk from increased intakes of folate. The agency is also aware of the lack of safety data for long-term intakes of folate between 1 and 5 mg/day, the existence of limited data regarding adverse effects of intakes below 1 mg, and the arguments regarding the lack of safety data on continuous exposure of body tissues to free circulating folic acid in oxidized form when intakes exceed 1 mg daily. The agency knows of no data that would support the long-term safety of continuous daily folate intakes of more than 1 mg and knows of no data to support a level of intake somewhat above or below 1 mg. FDA, however, notes that the value of 1 mg for a safe upper limit of daily folate intake could be modified if data were available to support such a decision. FDA solicits comments, particularly data, on this point.

The Folic Acid Subcommittee at its April 15, 1993 meeting supported the agency's use of 1 mg of folate daily as an upper intake limit for fortification, and the PHS recommendation states that women of childbearing age should not exceed intakes of 1 mg/day. A safe upper limit of daily folate intake of 1 mg was also discussed by experts who attended a recent CDC workshop on

surveillance for adverse effects of increased folic acid intakes. Those experts stated that there was little likelihood of problems at daily intakes lower than 1 mg, that the risk associated with continuous intakes of 5 mg and higher is well documented, and that the limited case reports and concerns regarding high circulating levels of free folic acid raised questions about safety of intakes between 1 and 5 mg daily (Ref. 59).

B. Risks to Pregnant Women

About 4 million pregnancies occur in the United States each year. In *Nutrition During Pregnancy* (Ref. 50), IOM stated that the safety of large doses of folic acid during pregnancy has not been systematically determined (Ref. 50). IOM noted that large doses of folic acid may inhibit the absorption of other nutrients by competitive interaction and can also obscure the diagnosis of onset or relapse of pernicious anemia, which IOM stated is extremely rare in women of childbearing age. IOM recommended modest supplementation for some segments of the U.S. population at risk of folate inadequacy. Such subpopulations include some pregnant women who lack the knowledge or financial resources to purchase adequate food; abusers of alcohol, cigarettes, or drugs; those with malabsorption syndromes; adolescents; and women bearing more than one fetus.

A potential risk of high folate intakes involves effects of high blood levels of free folic acid on the embryo during early gestation. The concern regarding the lack of safety data for increased doses of folic acid in pregnant women has been discussed in the scientific literature since the report of the successful MRC trial (Ref. 4). The principal investigator of that study (Ref. 4), in which women at high risk of a recurrence of an NTD pregnancy were treated with 4 mg folic acid daily, noted that the study did not have the power to ascertain the safety of such high level supplementation in the population studied.

Following publication of the results of the MRC trial (Ref. 4), Leeming et al. (Ref. 84) stated that while 4 mg of folic acid until 12 weeks of pregnancy may reduce the incidence of NTD's in women at high risk of recurrence, there may also be damaging effects. These authors suggested that substantial amounts of unmetabolized folic acid appear in the plasma after a single high dose, and that continuous high circulating levels of free folic acid may damage developing neural tissue during early embryonic development. They further noted that high levels of folic acid are not normally found in the circulation (Ref. 16). Scott et al. (Ref. 85) also suggested the seriousness of risk during early embryonic development, since folic acid is concentrated in crossing the placenta and accumulates in fetal tissue. Leeming et al. (Ref. 84) stated that while the fully developed brain may be protected from neurotoxic effects of high circulating levels of folic acid, no information is available as to whether developing neural tissue is similarly protected (Ref. 85).

The agency discussed uncertainties and lack of data regarding potential effects of high folic acid levels on the fetus and its tentative decision to propose a safe upper limit of folate intake of 1 mg/day with respect to safety for persons with vitamin B_{12}-related problems with the Folic Acid Subcommittee at its November 23 and 24, 1993 meeting. The Folic Acid Subcommittee did not believe that folate intakes less than 1 mg/day posed a risk to pregnant women. Support for this view is also provided by the fact that the NRC RDA for pregnant women has been set at 800 µg folate daily for many years. The agency is not aware of data showing that such intakes have posed risks to pregnant women. The agency, however, is not aware of any data showing safe use above this level. The agency has tentatively concluded that an upper limit of intake of 1 mg of folate/day is safe for pregnant women.

C. Persons With Epilepsy

There are approximately 2.5 million persons in the United States with epilepsy and an estimated 200,000 persons whose epilepsy is not controlled (Ref. 12). The possibility has been raised that high intakes of folic acid may reverse the effectiveness of anticonvulsant medications (Ref. 86) because folic acid and certain anticonvulsants compete with each other for receptors on brain cells. A potential concern is whether high intakes of folic acid exacerbate seizures in persons with uncontrolled- or drug-controlled epilepsy.

Most studies of the effects of folic acid in persons with drug-controlled epilepsy have involved institutionalized individuals. Their responses to very high doses of folate (e.g., generally 5 to 15 mg orally; 30 mg, orally, or 75 mg intravenously) have been variable. For example, while increases in fit frequency in response to oral folic acid in the range of 5 to 30 mg daily have been noted in several isolated cases (Refs. 87, 88, and 89), no such effects were found in several controlled studies including double-blind, crossover studies utilizing 15 to 20 mg folic acid/day in patients with drug-treated epilepsy (Ref. 90, 91, 92, 93, and 94). More recently, several studies of epileptic patients treated with Dilantin and given 3 to 5 mg folic acid daily for gingival hyperplasia for periods of 4 months to 1 year reported no change in seizure frequency (Bachman, 1989; Brown, 1991, cited on pages 216 and 217 of Ref. 12).

Based on its review of the available data, the agency has tentatively concluded that daily intakes of 1 mg of folate are not likely to interfere with the effectiveness of anticonvulsant medications used in the treatment of epilepsy. The available data were reviewed at the November 23 and 24, 1992 meeting of the Folic Acid Subcommittee (Ref. 12). The Folic Acid Subcommittee agreed that, based on the scientific data currently available, there is no indication that there is increased risk for patients with epilepsy with daily intakes of folic acid of up to 1 mg of folic acid (Ref. 12). Based on these factors, the agency has tentatively concluded that its decision to set an upper limit of intake of 1 mg of folate/day is safe for persons with epilepsy.

D. Persons Taking Drugs That Interfere With Folate Metabolism

Folate antagonists such as Methotrexate are used in the treatment of various cancers, including leukemias (Ref. 95). In addition, low doses of Methotrexate are currently used in the treatment of psoriasis, rheumatoid arthritis, and bronchial asthma. Other drugs that interfere with folate metabolism include Pyrimethamine, Trimethoprim, Triamterene, sulfasalazine, colchicine, phenytoin, and Trimetrexate (Ref. 95). Recognition of the therapeutic usefulness of these antifolate drugs for the treatment of psoriasis, rheumatoid arthritis, bronchial asthma, malaria, hypertension, Crohn's disease, gout, epilepsy, and AIDS has developed during the last 30 years. Taken together, these conditions affect significant portions of the general U.S. population (Ref. 95). The safety of significantly increased folate intakes by persons with these disorders, whether or not they are receiving antifolate medications, remains an open question (Ref. 96). In addition, the question of whether significantly increased intakes of folate would reduce the efficacy of these antifolate medications must also be considered.

Morgan et al. (Ref. 97) studied the effects of administration of 1 mg folate daily in patients with rheumatoid arthritis during low-dose Methotrexate therapy for 6 months. Administration of

the folic acid supplement significantly lowered toxicity scores for the Methotrexate therapy, without affecting efficacy of the therapy, as measured by joint counts, joint indices, and physician and patient evaluation of the disease activity. There has not been a controlled trial of the effects on Methotrexate toxicity or therapeutic effectiveness with the use of folic acid supplementation at doses higher than 1 mg daily. Some investigations have prescribed folic acid at doses higher than 1 mg/day for Methotrexate-treated rheumatoid arthritis patients (Refs. 98 and 99), but this use has been controversial because of potential effects on disease responses (Refs. 100 and 101).

The agency discussed the issue of potential effects of increased folate intakes on persons taking antifolate drugs for a number of medical conditions with the Folic Acid Subcommittee at its November 23 and 24, 1992, meeting. The agency noted that there is relatively little data on effects of increased intakes of folate by persons taking antifolate medications for treatment of inflammatory and other diseases. This topic was the subject of several comments submitted to the agency following the November 23 and 24, 1993, Folic Acid Subcommittee meeting.

A physician wrote to express concern regarding increased intake of folate and the possible adverse effects of such intake on patients with myositis and other rheumatic diseases who are taking the antifolate Methotrexate (Ref. 102). The physician noted that studies suggesting beneficial effects of increased folate intake by such patients were small, and that the effects of prolonged intakes of folate are uncertain. The physician also noted that the possible adverse effects of folate supplementation may be more severe in children undergoing treatment for rheumatic disease given their smaller mass and narrower margin of safety with Methotrexate therapy.

Another comment noted the controversy about the use of folate supplements in patients with rheumatoid arthritis treated with Methotrexate (Ref. 103). The comment stated that the concern about potential toxicity in children taking Methotrexate for treatment of juvenile rheumatoid arthritis was not supported, to the commenter's knowledge, by any data, and that the knowledge of human folate homeostasis is limited. The comment stated that because low-dose Methotrexate is now used in the treatment of psoriasis, asthma, inflammatory bowel disease, and juvenile rheumatoid arthritis, the issue of folate status takes on increased importance in several groups of patients. The comment stated that there was a need to develop sensitive, reliable, and inexpensive assessment tools for determining folate status. The comment urged FDA to carefully weigh any decision about food fortification with folic acid until there is more understanding about the consequences of folate repletion and depletion on human health.

As noted above, the American College of Rheumatology, in a statement regarding use of folic acid in conjunction with the antifolate, Methotrexate, in patients with arthritis, stated that consumption of folic acid at a dose of 1 mg/day does not appear to inhibit the efficacy of low-dose weekly Methotrexate therapy in rheumatoid arthritis (Ref. 53).

With respect to adverse effects of increased folate intakes to persons taking antifolate medications, the agency has tentatively concluded from its review of the limited data currently available (see above), its discussions with the Folic Acid Subcommittee, and the comments that it received, that its tentative decision to set a safe upper limit of 1 mg folate/day for all population groups will not increase risk of adverse effects to persons taking antifolate medications because doses of up to 1 mg folate/day have not been reported to reduce the effectiveness of medications that interfere with folate metabolism.

The agency is, however, requesting scientific data and information on this matter because there are large numbers of patients taking low levels of antifolate drugs on a chronic basis, and the current scientific literature on potential adverse effects of significant increases in folic acid intakes (e.g., intakes greater than 1 mg/day) is very limited.

E. Others

Competitive interactions between folic acid and other nutrients have also been reported (Refs. 104 and 105). There have been contradictory reports related to potential adverse effects of folic acid supplementation on zinc status. Simmer et al. (Ref. 105) measured zinc absorption during the second trimester in 10 healthy pregnant women with normal medical histories and in ten healthy volunteers and found that oral iron-folate supplements containing 100 mg ferrous iron and 350 µg folate reduced the intestinal absorption of an oral dose of 25 mg zinc (provided as 100 mg zinc sulfate). Simmer et al. (Ref. 105) also reported that folate alone decreased zinc absorption. The study of Simmer et al. (Ref. 105) did not include a control group of pregnant women.

Some other studies have suggested that folic acid supplements interfere with intestinal zinc absorption in humans and animals (Refs. 106 and 107). Ghishan et al. (Ref. 104) described the formation of zinc-folate complexes in the intestine and suggested this as a possible mechanism for folate-zinc interactions. However, other studies have provided inconsistent findings relating to a zinc-folate interaction. For example, in a study of 450 pregnant women, Mukherje et al. (Ref. 108) found a high degree of correlation between elevated serum folate, low plasma zinc, and the occurrence of fetomaternal complications, while another study of 285 pregnant women did not provide evidence of deleterious effects of folic acid supplementation on maternal zinc nutriture (Ref. 109). Butterworth and Tamura (Ref. 96) and Zimmerman and Shane (Ref. 110) have reviewed the varying results of potential effects of folate on zinc status reported in the literature. Zimmerman and Shane (Ref. 110) concluded that there is no convincing evidence that folate supplementation compromises zinc status in pregnancy. They stated, however, that until the issue is clarified, it may be prudent to ensure adequate maternal dietary zinc intake during folic acid supplementation, particularly in women receiving 4 mg folic acid/day. In summary, there have been no long-term studies to quantitate the effects, if any, of increased folate intake on metabolism of other nutrients.

The limited scientific data available on the topics outlined above were presented to the Folic Acid Subcommittee at its November 23 and 24, 1992 meeting. Based on its review of the scientific data currently available on interactions between folate and other nutrients or drugs, and its discussions with the Folic Acid Subcommittee and expert consultants, the agency has tentatively concluded that its decision to set an upper limit of daily folate intake of 1 mg for all population groups will not cause adverse effects because the available scientific data does not provide evidence for the occurrence of such effects at intakes of folate at levels attainable from usual diets. The agency also recognizes that because of the uncertainties in the data on the safety of folic acid intakes, some deviation (either up or down) from the proposed 1 mg limit may be warranted. The agency specifically requests data on this issue.

V. Addition of Folic Acid to Foods

If FDA adopts this proposal and authorizes a health claim on folate and

NTD's, it creates the likelihood that vendors will fortify their products with folic acid to qualify to make a claim. One of the prime ways that FDA has of protecting the public against risks created by the possibility of greatly increased fortification of the food supply is its authority to regulate the use of food additives.

FDA's current food additive regulation for folic acid (§ 172.345 (21 CFR 172.345)) provides that:

> Folic acid (folacin) may be safely added to a food for its vitamin property, provided the maximum intake of the food as may be consumed during a period of 1 day, or as directed for use in the case of a dietary supplement, will not result in daily ingestion of the additive in excess of 0.4 milligram for foods labeled without reference to age or physiological state; and when age or the conditions of pregnancy or lactation are specified, in excess of 0.1 milligram for infants, 0.3 milligram for children under 4 years of age, 0.4 milligram for adults and children 4 or more years of age, and 0.8 milligram for pregnant or lactating women.

However, the agency recognizes that, as currently written, the regulation lacks the necessary detailed guidance to enable vendors of foods to decide which foods are appropriate for fortification, and the levels at which folic acid can be added. Nothing in FDA's current food additive regulation would prevent the addition of folic acid to virtually any food. As currently written, the food additive regulation is not a practical way to regulate the folic acid content of the food supply or to assist consumers in achieving specified folate levels in their diets.

In addition to its authority to regulate the use of food additives, and specifically with respect to the safety of substances that are the subject of health claims, the agency cannot authorize a health claim if ingestion of the substance that is the subject of the claim will increase the risk of a disease or a health-related condition in persons in the general population (see section 403(r)(3)(A)(ii) of the act). From the discussion above, it is clear that if the intake of folate is not limited, it can have such an effect in persons in the general population.

FDA has tentatively concluded, however, that a health claim for folate can be safely implemented if folic acid addition to the food supply is controlled through an amendment to the food additive regulation for folic acid. The agency is proposing to amend § 172.345 to set limitations for use of folic acid on a per serving basis; to allow for the addition of folic acid to foods for which there exists a standard of identity as authorized in the standard; and to make breakfast cereals and dietary supplements the only nonstandardized foods to which folic acid may be added. The description and documentation for these proposed actions are described below, and the specific actions are proposed in companion documents published elsewhere in this **Federal Register.**

The agency's objectives in considering safety issues are not limited only to consideration of how to safely authorize a health claim. Given the potential of folate to reduce the risk of NTD's, FDA has tentatively decided that, as a public health matter, it would also be prudent to provide for fortification of the food supply to increase the likelihood that all women of childbearing age will have adequate folate intakes. Because neural tube birth defects arise very early in pregnancy, and because many pregnancies are unplanned, women must have adequate folate intakes throughout their childbearing years to reduce the risk of this complication. Thus, fortification of staple foods is one means of increasing the likelihood that women will have adequate intakes of folate.

The agency's goal of developing a fortification program that will increase folate intakes by women in their childbearing years while preventing excessive intakes by other segments of the population creates significant issues that FDA must consider in addressing how best to develop a folate fortification plan. For example, in trying to meet the goal of increasing the folate intake of the target population, the agency must also consider the effects of fortification on the folate intakes of others outside the target population and on heavy consumers within the target population and take steps to ensure that safety concerns are not created. Conversely, limiting intakes of folate to levels that are clearly safe for the general population may make it difficult for many target women to reach their intake goals without significant changes in their dietary patterns. To work within these competing considerations, FDA has tentatively concluded that its overriding responsibility in developing a folic acid fortification policy is to establish a safe range of intake for all population groups and then to maximize folate intakes of the target population within this safe range.

A. Background: Fortification Policy

The addition of nutrients to specific foods has been an effective way of maintaining and improving the overall nutritional quality of the food supply. When fortification programs were first initiated, deficiency diseases were widespread in the U.S. population. Today, in part because of food fortification programs, deficiency diseases rarely occur in the general U.S. population.

To help implement these fortification programs, FDA established standards of identity for several enriched cereal-grain products that require fortification at specified levels with four nutrients, thiamin, riboflavin, niacin, and iron (6 FR 2574), (8 FR 9170), (15 FR 5102), and (17 FR 4453). The addition of these nutrients serves to replace milling losses and to supplement inadequate dietary intakes.

In 1974, the Food and Nutrition Board of the NRC (the Board) published its "Proposed Fortification Policy for Cereal-Grain Products" (Ref. 111). Using available food consumption data, the Board recommended expansion of the then-current enrichment program for cereal-grain products. The Board stated that nutrients should be added to all cereal-grain products wherever technically feasible, because cereal-grain products meet the criteria for carriers of nutritional fortification for most nutrients (Ref. 111). The Board identified fortification levels in cereal-grain products for a number of nutrients, including a recommendation that cereal-grain products be fortified with folic acid at a level of 0.3 mg/pound (70 µg/100 g). Fortification at this level would approximately restore the folate lost during milling.

Technical feasibility studies of aspects of the recommended fortifications were carried out following the 1974 NRC recommendation, with results presented at a workshop in 1977 (Ref. 112). Levels of folate in milled wheat flours, determined during baseline studies, were found to be 0.076±0.018 mg/pound (mean±SD; 76±18 µg/pound; mean=18 µg/100 g) (Ref. 112). Thus, a level of fortification of 0.3 mg/pound (70 µg/100 g) represents an approximate fourfold increase above levels of folate found in milled wheat flours. The agency has used the NRC report (Ref. 111) and the data provided at the 1977 workshop (Ref. 112) as a general guide in developing its options for fortification. The agency recognizes that this report and data are about 20 years old. However, to the agency's knowledge, no more recent report or data directly applicable to fortification issues are available.

In 1980, FDA codified in § 104.20 (21 CFR 104.20) a uniform set of principles to serve as a model for the rational fortification of foods. This set of principles is generally followed by the agency in promulgating regulations for

enriched foods. The agency defined "fortification" as the addition of discrete nutrients, such as vitamins, minerals, or proteins, to foods (45 FR 6323, January 25, 1980). The agency stated that fortification should serve as a means of maintaining and improving the overall nutritional quality of the food supply.

The agency stated that fortification is appropriate to correct a dietary insufficiency recognized by the scientific community (that is, available scientific data must demonstrate that the nutrient deficiency clearly exists within a defined population); to restore nutrients lost in processing; to balance the vitamin, mineral, and protein content of a food based on caloric density; to avoid nutritional inferiority; and to comply with an existing regulation (§ 104.20). In addition, the agency stated that foods that are appropriate vehicles for fortification are those that are consumed by a significant portion of the population in an amount adequate to meaningfully increase intakes of a nutrient, and those in which the nutrients will be provided in a bioavailable form and in which nutrients will be stable under normal conditions of storage and use. The agency also stated that the level of nutrients added in fortifying a food must preclude toxic effects (§ 104.20).

As noted above, the PHS recommendation identified fortification of the general food supply as one approach for delivering folate to women of childbearing age. At its November 23 and 24, 1992, meeting, the Folic Acid Subcommittee extensively discussed the advantages and disadvantages of folic acid fortification. Several members expressed concern regarding potential adverse effects of increased folate intakes if fortification of the food supply were not adequately controlled. They noted that everyone, both target and nontarget populations would unavoidably be exposed to higher folate intakes.

The Folic Acid Subcommittee recognized the need for adequate folate nutriture throughout the childbearing years, and the fact that, to be effective, folate must be provided in the periconceptional interval. In this context, the members of the Folic Acid Subcommittee discussed the advantages of fortification: (1) The availability of increased folate to all women in the target population, regardless of economic or educational status, and (2) the passive nature of fortification in increasing folate intakes (i.e., exposure occurs without the need to change food selection practices or to remember to take a supplement). The Folic Acid Subcommittee recommended that FDA develop a fortification strategy such that 90 percent of women of childbearing age (10th percentile of intake) could receive at least 400 µg of folate (0.4 mg)/day from all sources, while preventing excessively high folate intakes by nontarget groups.

At its April 15, 1993, meeting, the Folic Acid Subcommittee reviewed FDA's analyses of possible fortification scenarios. Following further discussion, six of nine Folic Acid Subcommittee members supported some fortification of the food supply, although they differed as to whether a level of 70 or 140 µg/100 g of flour was an appropriate base level. Three members were opposed to any fortification. Those in favor of fortification generally stated that this method had the capability of providing increased folate to the greatest number of women in the target population. Those opposing fortification expressed concern about the amount of uncertainty regarding the potential adverse effects and intake estimates.

FDA has tentatively concluded that implementation of a fortification plan for addition of folic acid to the food supply can effectively increase the folate intakes of women of childbearing age to assist them in reducing their risk of having an NTD-affected pregnancy. The agency's tentative conclusion is based on the following:

(1) Because the neural tube forms and closes within the first 4 weeks of pregnancy, folate is needed before conception and during early pregnancy, often before a woman knows that she is pregnant, if it is to have a beneficial effect on risk of NTD's;

(2) About half of the pregnancies in the United States are unplanned (Ref. 113);

(3) Use of a supplement on a daily basis throughout their approximately 30 years of childbearing potential may be a problem for many women, either because of their inability to afford such supplements or their failure to take them on a daily basis; and

(4) Fortification has the advantage of providing folic acid in a continuous and passive manner. For example, a low level of fortification in foods consumed with great frequency would increase the likelihood of obtaining adequate folate on a daily basis.

Thus, the agency is proposing to fortify the U.S. food supply with folic acid as an apparently effective means for improving the folate nutriture of women in their childbearing years. This proposal is consistent with the PHS recommendation and with the views of a majority of the members of FDA's Folic Acid Subcommittee. In implementing this program, however, the agency is mindful that development of strategies involving fortification of the general food supply requires careful consideration of potential adverse effects of such proposed fortification on the entire population. Authorization of a health claim for fortified or other folate-rich food also requires resolution of concerns about potential adverse effects of increased folate intakes.

B. Safe Fortification: Upper Limit of Folate Intake

Under section 409(c)(3)(A) of the act (21 U.S.C. 348(c)(3)(A)), the so-called "general safety clause," a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe. Sections 409(c)(5)(A) and 409(c)(5)(B) of the act state that the probable consumption of a food additive, and the cumulative effect of the additive in the diet of humans, may be considered in determining whether a proposed use of a food additive is safe.

The agency has tentatively decided to use 1 mg (1,000 µg)/day of total folate intake as the safe upper limit for such intake. Total folate includes both the naturally occurring pteroylpolyglutamates found in foods and the folic acid (pteroylglutamic acid) used as a fortificant in conventional foods and as a source of folate in dietary supplements and breakfast cereals. The agency's tentative conclusion to use 1 mg/day as the safe upper limit is based on: (1) The scientific evidence and discussion of experts that there are no data to ensure that adverse effects are not likely to occur at daily intakes of 1 mg and above, (2) the PHS recommendation that women of childbearing age should not exceed intakes of 1 mg (1,000 µg) of folate/day (Ref. 11), (3) the support by the Folic Acid Subcommittee of FDA's use of 1 mg of total folate/day as a safe upper limit guide for fortification (Ref. 58), (4) the uncertainties in food intake estimates and the difficulty in correcting for bioavailability, and (5) the need for some margin of safety between estimates of intakes and the safe upper limit of daily intake. A further discussion of how the agency arrived at this proposed level follows.

1. General

The agency considered the following factors in determining how to identify a safe upper limit of daily intake of folate:

a. *Current range of daily intakes.* FDA's estimates of current intakes from foods alone (Table 4) show that, across all population groups, the range of daily folate intakes is 110 to 200 µg/day for

low consumers and 350 to 560 µg/day for high consumers. Corresponding folate intakes from foods and dietary supplements are 150 to 220 µg/day for low consumers and 470 to 810 µg for high consumers.

b. *Recommended Dietary Allowances.* The NRC RDA's are defined as the levels of intake of essential nutrients that, on the basis of scientific knowledge, are judged by the Board to be adequate to meet the known nutrient needs of practically all healthy persons. The RDA's are neither minimal requirements nor necessarily optimal level of intake. Rather, the RDA's are safe and adequate levels (incorporating margins of safety intended to be sufficiently generous to encompass the presumed variability in requirement among people) reflecting the state of knowledge concerning a nutrient, its bioavailability, and variations among the U.S. population. RDA's for folate ("folacin") for various age groups have been between 100 and 400 µg, except for pregnant or lactating women, since 1968 (Refs. 46, 47, and 48 in 58 FR 2606).

c. *Current fortification practices.* Because standards of identity for cereal-grain products, fruit juices, and dairy products have not permitted or required the inclusion of folic acid, and because the current food additive regulation for folic acid imposes a limit of 400 µg (0.4 mg)/day on folic acid added to dietary supplements labeled for use by persons 4 years and older and a limit of 400 µg (0.4 mg)/day on folic acid added to breakfast cereals, there has not been widespread fortification of foods in the United States with folic acid. Thus, daily folate intakes by persons in the general population have apparently been below 1 mg.

2. Differences in Bioavailability Between Free Folic Acid and Food Folates

It is well recognized that the bioavailability of free folic acid, the form included in fortified foods and in dietary supplements, is severalfold higher than that of naturally occurring food folates. Estimates of the increased bioavailability ("potency") of free folic acid relative to food folates range from at least twofold to fourfold or greater (Ref. 45 in 58 FR 2606). The bioavailability of folates in foods ranges from approximately 25 to 75 percent depending upon a variety of factors that are incompletely understood. The majority of food folates occur as reduced folylpolyglutamates (i.e., forms that contain a number of glutamate residues), and the glutamates must be cleaved by intestinal conjugase before absorption.

Folate utilization may be reduced under conditions that inhibit conjugase activity and by natural conjugase inhibitors found in certain foods (Ref. 114). Crystalline folic acid, the oxidized monoglutamate form of the vitamin and the form used in food fortification and in dietary supplements, is generally assumed to have a bioavailability of approximately 100 percent. However, folic acid is likely to take on the bioavailability of folate in its food vehicle and that of the overall meal in which it is consumed because it binds to food constituents such as proteins and carbohydrates (Ref. 115). Additionally, consumers vary in whether they take folic acid supplements with or without food and in the type of beverage that they consume with supplements taken between meals. Thus, the bioavailability of folic acid added to foods in conventional food form or consumed from supplements could range from close to 100 percent if taken between meals to 25 percent or less if consumed as part of a meal containing folates of low bioavailability.

At its November 23 and 24, 1992, meeting, the Folic Acid Subcommittee discussed whether some adjustment should be made for variations in bioavailability of different sources of folate (Ref. 12). There was some discussion as to whether different forms of folate should be weighted differently in estimating a safe daily intake and in determining their effectiveness in reducing the risk of NTD's in women in the target population. This issue was largely unresolved at that time.

3. Safe Upper Limit of Intake

Based on the considerations above, the agency has tentatively decided to use 1 mg (1,000 µg)/day of total folate intake as the safe upper limit for achieving folate intakes.

The agency recognizes that the use of 1 mg as the upper intake limit is not without controversy. This subject engendered considerable discussion at FDA's November 23 and 24, 1992, Folic Acid Subcommittee meeting and, as noted above, was largely unresolved at that time. It also has been the subject of several comments received subsequent to the November 1992 meeting.

One question is whether the 1 mg daily limit should be based on total folate (i.e., food folates plus folic acid from fortified foods and supplements), or whether the 1 mg daily limit should be based only on folic acid from fortified foods and supplements (i.e., intake of folic acid above the background of intake of food folates). Proponents of the latter position contend that the data showing potential safety concerns above 1 mg daily are based only on administration of free folic acid and do not take into account background food folate intakes (Ref 13). They suggested that safety concerns are not well documented (Ref. 13), and that daily limits of folic acid intake higher than 1 mg/day are needed because folate intakes from fortification options limited by a 1 mg/day ceiling would be too low to be effective in providing sufficient folate to reduce the risk of NTD's for any but a small fraction of the target population of women of childbearing age (Ref. 13)

Conversely, an expert speaker at the November 1992 meeting expressed concerns about intakes in excess of 1 mg folate/day by individuals, particularly those individuals over 50 years, who may be at risk of vitamin B_{12} deficiency (Ref. 116). This speaker noted that there is no evidence to support the position that risk to the general population is negligible as long as food fortification provides less than 1 mg (1,000 µg) of dietary folate daily. The expert speaker urged the agency, if it proceeded with fortification plans, to develop a surveillance mechanism that could provide early identification of any adverse effect of fortifying the diets of most Americans with folate. FDA notes that it is working with other agencies within PHS to improve surveillance mechanisms for monitoring possible adverse reactions to increased folate intakes.

FDA has carefully considered the conflicting views on the safe upper limit of intake for folate. Based on the current state of the scientific evidence and the factors listed above, FDA tentatively concludes that an upper safe limit of intake of 1 mg folate is necessary to ensure the safety of the food supply. FDA has also tentatively concluded that the safe upper limit of 1 mg daily should be based on folate, rather than on added folic acid, and that it should not be adjusted for bioavailability factors. FDA's use of this value is based on its review of the scientific record, on its discussions with the Folic Acid Subcommittee and the fact that much of the concern that has been expressed about intakes above 1 mg folate/day has not been qualified based on the source of the folate. The upper limit of safe intake that FDA is proposing represents the agency's best scientific judgment at this time. FDA solicits comments and data on this tentative judgment. The agency recognizes the significance of this proposed upper limit to its analysis of options for fortification. The agency also recognizes that this value may need to be adjusted based on comments that

it receives. FDA will carefully consider any data that it receives on the issue of the safe upper limit of daily folate intake and will make necessary adjustments in this level based on its review of the data that are submitted.

C. Models Used and Fortification Options Evaluated

In developing its options for fortification and in reaching its tentative conclusions, the agency considered both effectiveness in reaching most women in the target population and maintenance of a safe level of daily intake (that is, an intake of 1 mg or less) for "high consumers" of folate both within the target population and in the general population. The agency considered the following in reaching its tentative conclusions:

(1) The expected daily intakes of "high consumers" of all age and gender groups and special risk groups must be evaluated for safety because the entire population will be passively and continuously exposed to folic acid in a fortified food supply;

(2) The effectiveness of a fortification option in reaching the target population can be evaluated by examining intakes at the lower end of the estimated intake distribution curve;

(3) Because estimates of folate intake from survey data are underestimates of true intakes because of the very low calorie intakes associated with some reported intakes, appropriate adjustments in intake distributions may be necessary; and

(4) Bioavailability cannot be meaningfully factored into fortification scenarios because issues of bioavailability are very complex, and no systematic data are available on many of the factors that affect bioavailability.

FDA presented estimates of the potential effects of food fortification on folate intakes to the Folic Acid Subcommittee at its November 23 and 24, 1992, meeting and in its final rule denying a health claim on folic acid and NTD's (58 FR 2606 at 2621). The estimates were based on intakes resulting from fortification of foods at specified levels of folic acid on a "per serving" basis. The "folic acid per serving" approach had the advantage of being rapidly performed, while reflecting changes in intakes that could occur with various fortification scenarios. This initial approach, however, needed refinement. FDA provided refined estimates, which were based on fortification of foods (e.g., fruit juices, dairy products) and food ingredients (e.g., cereal-grain products), to the Folic Acid Subcommittee at its April 15, 1993, meeting. In general, both types of estimates provided similar results regarding the effects of fortification on estimated folate intakes.

1. Data Base Chosen

The agency used USDA's 1987 to 1988 NFCS data base (Ref. 117) to estimate the potential effects of fortification of specific components of the food supply on folate intake by women in their childbearing years and by persons in the general population. The NFCS was designed to produce nationally representative estimates of food and nutrient intakes. Each respondent provided 3 days of dietary data. Such data provide better estimates of individual food intake than do, for example, 24-hour recall data, or food frequency data. In addition, for each respondent, the survey provided general information about supplement intake and brand-specific information about consumption of breakfast cereals.

FDA used the 1987 to 1988 NFCS because it provides the most recent nationally representative food consumption data available for all age/sex groups. Other recent food consumption surveys that FDA considered using lacked data on older children, adolescents, and older adults (for example, 1985 and 1986 USDA CSFII). Unlike other surveys, the 1987 to 1988 NFCS also includes brand name information on commonly fortified foods such as breakfast cereals, thereby allowing an estimate of folate intake from this category of foods based on manufacturers' current fortification practices. Thus, the 1987 to 1988 NFCS provided data that were particularly pertinent to the agency's needs and that were not available in other more recent surveys.

A disadvantage of using the 1987 to 1988 NFCS is the caution needed in interpreting the results because of the low response rate (Ref. 118). FDA considered using other national surveys with higher response rates (i.e., the 1977 to 1978 NFCS or 1976 to 1980 NHANES were considered), but they were judged by the agency to be too outdated to be useful or to lack the information necessary to reflect current folate fortification of breakfast cereals.

The low response rate of the NFCS may suggest a possible source of bias in the agency's estimates. However, an expert panel convened to assess the impact of the low response rate in this survey concluded that the presence or absence of a nonresponse bias could not be demonstrated with certainty (Ref. 118), and distribution data of the type used in the NFCS analysis have generally been consistent with results from other nationally representative surveys with higher response rates.

2. General Approach

The approach that FDA used to estimate folate intakes is based on the most relevant regulatory and food manufacturing units, e.g., servings of breakfast cereals, grams of cereal-grain products used as food ingredients, or measured portions of fruit juices or dairy products. Using information from NFCS respondents on the types and amounts of foods that they consumed over a 3-day period, general information on their use of dietary supplements and breakfast cereals, and a folate composition data base that provided specific information on folate content of foods and food ingredients (Ref. 119), FDA summed the total folate intake from all sources for each individual and obtained a value for mean folate intake per day. The agency used this average value from 3 days of data as the "usual" intake for an individual. FDA calculated distributions of folate intakes by age/sex groups from these values. The agency used the data to estimate the potential impact of various fortification options by altering the folate composition of selected foods and ingredients in the data base. For example, the agency recalculated intake estimates to determine the intake levels if all cereal-grain products contained 70 µg folic acid/100 g, or if selected juices or dairy products contained 140 µg folic acid/100 g.

The results of such estimations reflect likely changes in total folate intake if selected foods are fortified at one of several levels. These estimations were all based on current dietary patterns. The agency is aware, however, that individuals may change their dietary patterns by selecting folate-rich foods in response to a health claim. However, the agency knows of no way to estimate the magnitude of such changes in dietary patterns or to estimate their net effects in increasing folate intakes.

The NFCS provided qualitative information on dietary supplement use. In deciding whether to assign a folate contribution (i.e., value) to a reported supplement used, FDA considered whether the supplement was likely to contain folic acid. The response categories that FDA treated as being likely to contain folic acid included: "multivitamin," "multivitamin with iron or other minerals," "other combination of vitamins and minerals," or "other single vitamins/minerals." FDA considered the following response categories as representing supplements that were not likely to contain folic acid:

"combination of vitamin C and iron," "vitamin C," "iron," or "calcium."

In NFCS, consumers reported the frequency with which they consumed supplements described in the general terms above as "every day" or "almost every day," "every so often," or "not at all." Current marketing practice is to include folic acid in supplements labeled for use without reference to age or physiologic state at 400 µg. Thus, FDA included in daily folate intakes a value of 400 µg for those respondents 4 or more years of age who reported that they took supplements "every day" or "almost every day" and a value of 200 µg/day for those who said they took supplements "every so often." For persons 1 to 3 years of age who reported that they took supplements "every day" or "almost every day," FDA assigned an intake value of 200 µg/day. FDA assigned an intake value of 100 µg/day for persons 1 to 3 years of age who responded that they consumed supplements that might contain folic acid "every so often."

a. *Foods chosen for consideration as vehicles for fortification.* FDA expects that there will likely be a significant increase in consumption of folate by women in their childbearing years, and by the general population, if a health claim were to be authorized because manufacturers will add folic acid to their products in order to claim that these products are useful in reducing the risk of birth defects, and consumers will have point-of-purchase information available to them in making decisions regarding food selections. In its January 1993 final rule (58 FR 2606), the agency presented estimates of intakes of total folate and free folic acid that might result from uncontrolled fortification of foods with folic acid (i.e., FDA considered for these estimates that foods were fortified to the current unit limit of 400 µg) (58 FR 2606 at 2621; Table, Estimates A and B). The estimates showed that daily intakes of total folate of low consumers and high consumers could reach 4,700 µg (4.7 mg) and 9,100 µg (9.1 mg), respectively, if such fortification were to occur. Intakes of multiple doses of free folic acid in the form of dietary supplements and from its increased presence in the food supply could result in daily intakes of more than 3 mg (3,000 µg) by low consumers and approximately 7 mg (7,000 µg) by high consumers (58 FR 2606 at 2621; Table, Estimates A and B). These estimated intakes significantly exceed the agency's safe upper limit of intake of 1 mg of folate/day.

After reviewing these results, the agency tentatively concluded that limitations on the types of foods that might be fortified, and on the amounts of folic acid that might be added to such foods, were necessary to prevent unsafe levels of folic acid fortification of the food supply.

In examining options for providing folate to women of childbearing age through food fortification, the agency considered various options including allocation of folate to products such as cereal-grain products, fruit juices, and dairy products. It also considered current practices with respect to inclusion of folic acid in breakfast cereals and in dietary supplements.

In selecting foods to consider as vehicles for fortification, the agency started with the basic principle that fortification of staple products that are commonly consumed in significant amounts by virtually all members of the target population is most likely to effectively result in increased intakes of a specific nutrient by the target population. The agency notes that cereal-grain products were the fortification vehicle recommended by the Board (Ref. 111). These foods are consumed on a daily basis by more than 90 percent of women of childbearing age (Ref. 120).

In identifying specific cereal-grain products for fortification, the agency considered those products with established standards of identity: Enriched bread, rolls, and buns; enriched wheat, corn, and rice flours; enriched corn grits and enriched corn meals; enriched farinas; enriched rice; enriched macaroni products; and enriched noodle products (21 CFR parts 136, 137, 139). The dry (i.e., uncooked) cereal-grain products that were part of the fortification scenarios included wheat flours, rice, farinas, corn meals, corn grits, and macaroni, spaghetti, and noodles. Under standards of identity, the addition of specified amounts of certain nutrients to such products allows them to be labeled as "enriched." Folic acid is not currently among the nutrients permitted or required to be included in "enriched" products. To permit or require addition of folic acid to such products, the standards of identity for specific cereal-grain products must be amended (see companion document published elsewhere in this **Federal Register**).

Because of data showing that 90 percent of women of childbearing age report consumption of cereal-grain products on a daily basis (Ref. 120), all fortification options the agency considered included fortification of cereal-grain products.

FDA also considered including breakfast cereals in its fortification strategy because they represent a traditional source of many nutrients, including folic acid, for those who consume them. Breakfast cereals are also consumed by many women of childbearing age. Folic acid can be readily added to breakfast cereals. Its level in these foods is limited only by the limits established in the food additive regulation (21 CFR 172.345). Similarly, because approximately 30 to 40 percent of women of childbearing age use dietary supplements (Ref. 121), the agency also included the availability and continued use of dietary supplements in fortification options.

The agency was concerned that some women of childbearing age may not eat sufficient amounts of cereal-grain products, or breakfast cereals, or use dietary supplements, and consequently, fortification options limited to these folate sources might not be able to significantly increase the folate intakes of such women. Other foods with standards of identity that are frequently fortified include dairy products and juices (including milk, yogurt, fruit juices, and canned fruit nectars). Folic acid is currently not among the nutrients that are permitted or required in these foods under applicable standards of identity. Thus, in some of the fortification options, the agency evaluated the additional impact on folate intakes of fortification of both fruit juices and dairy products.

b. *Folate composition data.* FDA used an ingredient file prepared by the USDA's Human Nutrition Information Service (HNIS) to estimate total folate intakes (Ref. 119). Data in the ingredient file was based either on the levels of folate in foods and their ingredients in the U.S. food supply or on various changes that reflected the effects of several fortification options. Since the USDA ingredient file identified the grain ingredients of interest for all food categories in the survey, FDA was able to use the data in the file to estimate the total dietary effects of fortifying these grain ingredients. For example, the file allowed the agency to determine the effect on folate intakes that could result from fortifying the flour consumed in breads, rolls, buns, or cake as well as the flour consumed as a component of a frozen dinner (e.g., pizza crust, noodles, rolls, or breadings).

In one set of analyses, FDA estimated the effects of fortification on intakes by assuming fortification of cereal-grain products with 0.070, 0.140, and 0.350 mg folic acid/100 g. The value of 0.070 mg/100 g (0.30 mg/pound) is the amount recommended by the Board in 1974 (see above). Values of 0.140 and 0.350 mg/100 g represent twofold and

fivefold increases, respectively, above the Board's recommended level.

In a second set of analyses of potential intakes from fortified foods, the agency applied the levels of fortification used above to a broader range of food products including certain dairy products and fruit juices. Examples of dairy products and fruit juices to which fortification levels were applied included fluid cows' milk, reconstituted dry milk, condensed and evaporated milks, yogurts, and fruit juices such as orange, grapefruit, lemon, pineapple, apple, and grape.

Many breakfast cereals (dry ready-to-eat and cooked), as defined in 21 CFR 170.3(n)(4), are currently fortified with 100 µg of folic acid/labeled serving (25 percent of the RDI). Other breakfast cereals contain 35 to 45 percent of the RDI for folate (140 to 180 µg/labeled serving), while a limited number contain 100 percent of the RDI for as many as 17 minerals and vitamins, including folic acid (RDI for folate, 400 µg). The NFCS provided brand-specific information about breakfast cereal consumption. Values for folate content of these breakfast cereals were obtained from brand-specific data provided in the USDA data base. For about the 50 top-selling ready-to-eat dry cereals, in instances in which the current folic acid content of the breakfast cereal (identified from a review of food labels in a local supermarket) differed from the value used in the USDA data base, FDA updated the USDA data base values with the more recent values. Thus, values assigned to these breakfast cereals were generally reflective of what is currently in the marketplace. (Note: This correction was not applied to cooked breakfast cereals because of lack of brand-specific information.)

For dietary supplements, FDA assumed current marketing practices of including 400 µg (0.4 mg) folic acid/daily dose for supplements labeled without reference to age or physiologic state. The agency added a value of 400 µg/day to folate intakes for regular use of folic acid-containing supplements and added a value of 200 µg/day to folate intakes for irregular use of folic acid-containing supplements.

With the availability of health claims for folic acid and NTD's, the breakfast cereal market is likely to increase folic acid fortification to higher levels than are currently used. For purposes of considering possible effects of changes in levels of fortification of breakfast cereals on estimates of total daily folate intake, FDA considered two possibilities: (1) All breakfast cereals would be fortified to a level of 100 µg folic acid/serving (i.e., 25 percent of the RDI/serving); and (2) all breakfast cereals would be fortified to a level of 400 µg folic acid/serving (i.e., 100 percent of the RDI/serving). The agency estimated folate intakes that might result from these two possibilities in a food supply in which cereal-grain products were also fortified (i.e., the agency used levels of cereal-grain fortification of 0.07, 0.140, and 0.35 µg folic acid/100 g for these estimations).

c. *Analysis.* FDA conducted all data analyses using the procedures of Statistical Analysis System (SAS). In addition, the agency weighted all of the results using factors provided with the data tapes that were designed to provide results representative of the U.S. population. Results were presented as distributions of average daily intakes of folate by age/sex groups.

FDA evaluated each fortification option by examining folate intakes at the low end of the distribution curve for the target population (hereafter referred to as "low consumers"). Thus, the higher the folate intake of low consumers in the target population, the more effective the fortification option would be in meeting the folate intake goals for the target population. The values for "low consumers" represent the minimum intakes for target women.

FDA evaluated the safety of intakes that would result from a particular fortification scheme by examining estimated folate intakes at the high end of the intake distribution curves (hereafter referred to as "high consumers"). Obviously, the highest intakes represent the greatest potential risks.

3. Reasonableness of Results: Possible Sources of Error in Intake Estimates

a. *Underestimation of food intake.* Food intake data frequently underestimate the actual food intake of respondents (Ref. 122). Clinical studies have shown substantial discrepancies between food intake reported by volunteers and intake subsequently determined to be required for weight maintenance. An average underreporting of 18 percent below maintenance food intake for men and women was found in one study of 266 volunteers (Ref. 122).

To assess the reasonableness of the estimated folate intakes from the 1987 to 1988 NFCS, the agency compared mean energy (calorie) intakes of survey respondents as calculated from reported food intakes to energy requirements estimated by the Food and Nutrition Board of NAS (Ref. 123) for various sex/age groups. In the 1987 to 1988 NFCS, calculated mean energy intakes of women 19 to 50 years, based on 3-day dietary data, were about 1,500 calories, whereas the most recent estimated average energy requirement for this gender/age group is 2,200 calories. The reported intakes represent about 70 percent of the average required intake, or an average reported energy intake about 30 percent below the most recent average energy allowance. Although FDA frequently uses 90th percentile intakes to evaluate intakes of high consumers (Ref. 124), in the present analysis, the 95th percentile for energy more closely corresponds to the upper range of energy requirements. Conversely, at the low end of the distribution curve, energy intakes based on reported food patterns are so low (approximately 1,200 calories for women of childbearing age) that normal weight maintenance would not be possible. Such diets could not be maintained, therefore, for more than short periods of time and are unlikely to represent "usual" intakes. FDA therefore used the 25th percentile intakes to estimate the level of folate intake that would be achieved by "low consumers," and the 95th percentile intakes to estimate the level of intake that would be achieved by "high consumers." The agency considers the adjusted intakes that it used to represent a reasonable intake range over time by most persons in an age/sex group. The agency also notes that in adjusting folate intake estimates to correct for underreporting of food intake, it assumed underreporting both for conventional foods and dietary supplements.

To evaluate possible bias because of the high nonresponse rate of the 1987 to 1988 NFCS, FDA compared the estimated mean daily intake of folate without fortification options or supplement use for women 19 to 50 years in the 1987 to 1988 NFCS (i.e., 189 µg folate/day) to mean daily folate intakes reported for this gender/age group in two other recent USDA surveys that had better response rates. The 1986 Continuing Survey of Food Intake by Individuals (CSFII) (Ref. 125) reported a mean daily intake of folate of 193 µg and the 1985 CSFII reported a mean daily folate intake of 189 µg (Ref. 126). Thus, results from these three surveys are comparable.

b. *Underestimation of folate content of foods.* There is general agreement that the methods currently used for folate analysis in foods are unsatisfactory (Ref. 115). Methods for liberation of naturally occurring folylpolyglutamates from complex food matrices and their hydrolysis to forms that can be accurately quantified by microbiological assay are difficult and are frequently

incomplete. Comparison of newer methods of sample preparation with older methods has revealed underestimates in the range of 20 percent for vegetables such as spinach and cauliflower and 50 percent for canned tuna (Ref. 115). Thus, commonly used methods of folate analysis may significantly underestimate the folate content of foods.

Additionally, to ensure that fortified foods (including breakfast cereals and dietary supplements) contain at least the amounts of nutrients, such as folic acid, that are declared in the label, manufacturers add excess amounts of the nutrients in preparing the foods. Since label values were used to define the folate composition of fortified breakfast cereals and dietary supplements, however, the values that are used are likely to understate the actual folate content of these foods.

c. *Overall reasonableness of intake estimates.* Taken together, the two factors of underreporting of food intake and underestimation of folate content of foods will likely result in significant underestimates in folate intakes. For example, if the magnitude of the combined underestimate was 30 percent, an estimated intake value of 750 µg of folic acid/day might actually be 940 µg/day, and an estimated intake of 200 µg/day might actually be 260 µg/day.

FDA has tentatively concluded that except for the crude adjustment to bring folate intake estimates in line with estimated energy needs, more sophisticated mathematical adjustments are not appropriate because they would attribute the estimates with more precision (or certainty) than is justified by the nature of the data upon which the estimates are based. In addition, because of the questions about bioavailability that are described above, the agency tentatively considers bioavailability to be too unpredictable to be factored into the analyses. Because of the multiple and variable sources of systematic error, the lack of information on the nature of interactions among these various sources of error, questions of variations in bioavailability of folate from various food and supplement sources under different meal/eating conditions, and the lack of systematic data addressing these questions, FDA was not able to identify a mathematical "adjustment" factor that it considered to be reasonably accurate or universally applicable. Therefore, the agency has not included any such factors when calculating estimates of folate intakes or in identifying appropriate levels of food fortification.

4. Results

a. *Estimates.* Estimates of current intakes of folate by low and high consumers with and without supplement use and the results of estimations for 12 options for fortifying cereal-grain products, fruit juices, and dairy products are shown in Table 4.

As shown in the results of intake estimations in Table 4, at all three fortification levels examined, when fortification included fruit juices and dairy products in addition to cereal-grain products (Estimate Nos. 9 to 11), intakes of high consumers exceeded 1,000 µg/day for most age groups even without supplement use. For example, if cereal-grain products, fruit juices, and dairy products were fortified with 350 µg folic acid/100 g (Table 4, Estimate Nos. 11 and 14), women of childbearing age who were "high consumers" could consume 480 to 830 µg or more of folate /day without supplement use and 630 to 870 µg or more of folate/day with supplement use, intakes consistent with the PHS recommendation. With this fortification level, estimated daily intakes of folate by children 1 to 10 years of age who were "high consumers" could reach 4,020 to 4,550 µg without supplement use and 4,260 to 4,620 µg/day with supplement use, values that are several multiples of their current RDA's and in excess of the upper safe limit of intake of 1,000 µg (1 mg). In addition, with this level of fortification, estimated daily intakes of folate by adults 51+ years who were "high consumers" could fall in the range of 2,670 to 3,240/day without supplement use and 2,900 to 3,750 µg/day with supplement use. These intakes exceed the upper limit of safe intake of 1 mg/day.

Fortification of cereal-grain products, juices, and dairy products with lower levels of folate (for example, at 70 µg/100 g) also results in daily folate intakes of high consumers in many groups in excess of 1 mg. FDA has tentatively concluded, therefore, not to allow fortification of dairy and juice products because such fortifications could result in potentially unsafe intakes by large segments of the population.

FDA then examined the effects of limiting fortification to cereal-grain products. The agency examined the same fortification levels: 70, 140, or 350 µg folic acid/100 g (Table 4). Pros and cons of these options are listed in Table 5. For reference purposes, examples of levels of folic acid that could be present in typical products (i.e., breakfast cereals and noodles manufactured from enriched flours, enriched breads) are also included in Table 5.

If cereal-grain products were fortified with 70 µg folic acid/100 g (Table 4, Estimate Nos. 3 and 6), folate intakes by adult population groups of "high consumers" would remain below 1 mg/day. If fortification of cereal-grain products was increased to 140 µg/100 g, intakes by adults 51+ years who were "high consumers" and who used supplements would approach 1 mg/day (Table 4, Estimate Nos. 4 and 7). Fortification of cereal-grain products at 350 µg/100 g (Table 4, Estimate Nos. 8) could result in estimated daily intakes by "high consumer" adults 51+ years of 980 to 1,100 µg when supplement use is included. When cereal-grain products are fortified at levels of 350 µg folic acid/100 g, daily intakes of folate by high consumers among children 1 to 3 years and 4 to 10 years are 670 and 1,030 µg with supplement use (Table 4, Estimate No. 8), values 2 to 3 times the RDA's for these age groups.

b. *Potential effects of fortification options for consumers who follow Federal government dietary guidelines.* As a further check on the reasonableness of the fortification options, FDA considered it prudent to evaluate the likely effects of fortification on folate intakes of consumers who follow government dietary guidance such as the U.S. Dietary Guidelines for Americans and the DHHS/USDA Food Guide Pyramid (Ref. 127). Fortification should not make compliance with the U.S. Dietary Guidelines unsafe.

The USDA Food Guide Pyramid recommends consumption of 6 to 11 servings of cereal-grain products/day, 2 to 3 servings of dairy products, 3 to 5 servings of vegetables, 2 to 3 servings from the meat group, and 2 to 4 servings of fruit. Estimates of folate intakes that could result from food consumption patterns consistent with Food Pyramid Guidelines with fortification of cereal-grain products at 70, 140, and 350 µg/100 g and breakfast cereals at 100 µg/serving (25 percent of the RDI) and 400 µg/serving are shown in Tables 6A and 6B. The estimates are based on consumption patterns at both the low (Table 6A) and high (Table 6B) ends of the USDA Food Pyramid Ranges.

FDA estimates that women who consumed 6 servings/day of cereal-grain products fortified with 70 µg folic acid/100 g and consumed a breakfast cereal fortified with 100 µg folic acid/serving would obtain 53 percent of the RDI (i.e., 210 µg/day) from these sources alone (Table 6A). Intake from these sources alone could be 510 µg folate/day if a breakfast cereal fortified with 400 µg folic acid were chosen instead of a breakfast cereal fortified with 100 µg folate. Consumption of 6 servings of

cereal-grain products fortified with 140 or 350 µg folic acid/100 µg and use of a breakfast cereal fortified with 100 µg folic acid/serving could provide 80 percent and 153 percent, respectively, of the RDI from these fortified food sources alone. Intakes from these sources alone could be 620 µg folate/day or 910 µg folate/day if a breakfast cereal fortified with 400 µg folic acid were consumed as part of a food supply in which cereal-grain products were fortified with 140 or 350 µg folic acid/100 µg, respectively.

FDA also estimates that women who followed a dietary pattern consistent with the upper end of the USDA Food Pyramid Range for cereal-grain products (i.e., 11 servings/day) and chose a breakfast cereal fortified with 400 µg of folate/serving (i.e., 100 percent of the RDI) could consume 620, 840, or 1,420 µg folate/day from these sources alone, depending upon whether cereal-grain products were fortified with 70, 140, or 350 µg folic acid/100 µg (Table 7B). Consumption of diets high in rich natural sources of folate such as specific vegetables and use of a dietary supplement of 400 µg folic acid could lead to daily intakes of folate of 1,670 µg, 1,890 µg, and 2,470 µg, with cereal-grain products fortified at 70, 140, or 350 µg/100 µg.

The estimates shown in Table 6A suggest that, without supplement use, consumers who followed even the low end of recommendations from the USDA Food Pyramid Food Guide could readily consume 420 or more µg of folate/day from all sources if cereal-grain products were fortified at 70 µg/100 g. For such "low" consumers who did not use supplements, daily intakes of folate from all sources could reach 530 or 820 µg/day with a food supply in which cereal-grains products were fortified with 140 µg or 350 µg folic acid/100 g, respectively.

c. *Potential effects of changes in fortification of breakfast cereals.* The agency also compared the effects on estimated intakes if there were a change in the current marketing practices for breakfast cereals. The agency considered effects on intakes if all cereals were fortified at levels of 100 µg/serving or 400 µg/serving, with results shown in Table 7. Since the great majority of breakfast cereals are currently fortified with 100 µg of folic acid/serving, comparisons of current intakes with those that might result from fortification of all breakfast cereals at 100 µg/serving show that they are essentially the same. However, the agency's estimates show that if all breakfast cereals were to be fortified at a level of 400 µg of folate/serving as part of a food supply in which a wide range of cereal-grain products were also fortified, intakes by high consumers in many population groups could approach or exceed the safe upper limit of intake of 1 mg. This result is true for some high consumers even without fortification of cereal-grain products and becomes more apparent as the level of fortification in cereal-grain products increases from 70 to 350 µg/100 g.

D. Tentative Conclusions—Options for Fortification

The estimates above suggest that fortification of standardized cereal-grain products at 70 µg/100 g or 140 µg/100 g, the availability of dietary supplements at 400 µg folic acid/unit, and the availability of breakfast cereals fortified at 100 µg folic acid/serving could provide folate intakes below 1 mg folate daily for most persons.

The agency notes that several presenters at the April 15, 1993 Folic Acid Subcommittee meeting recommended fortification of cereal-grain products at 350 µg/100 g because they felt that safety issues were exaggerated, and that intakes somewhat above 1 mg/day posed little or no hazard. Conversely, members of the Folic Acid Subcommittee who favored fortification were about evenly divided between fortification at 70 or 140 µg/100 g (Ref. 13). Those favoring fortification at levels of 70 or 140 µg folic acid/100 g stated that such levels could provide increased intakes of folate for women in their childbearing years while ensuring that intakes for nontarget groups in the population below 1 mg/day.

The level of fortification of cereal-grain products of 140 µg/100 g represents approximately twice the level recommended by the NRC in 1974 and is the higher of two levels proposed by the Folic Acid Subcommittee. The estimates for intake of folate from food by high consumers among adults 51+ years (those who are potentially at greatest risk of vitamin B_{12} deficiency) are 800 to 840 µg/day (Table 4, Estimate No. 7). However, if standardized cereal-grain products were fortified at 350 µg/100 µg, the estimated maximum intake from foods could be 980 to 1,050 µg/day (Table 4, Estimate No. 8). The agency has tentatively concluded that this level of cereal-grain fortification could provide intakes that exceed the safe upper folate intake limit and thus, because proposed fortification of cereal-grain products will provide continuous and unavoidable exposures, does not meet the requirement that a food fortification scheme be safe.

FDA tentatively finds, based on available data, that fortifying cereal-grain products with 140 µg of folic acid and allowing breakfast cereals to contain up to 400 µg of folic acid/serving will also result in daily folate intakes by significant portions of the population in excess of the safe upper limit of 1 mg/day. For example, intakes by high consumers in all adult population groups could reach (e.g., 950 to 980 µg/day for women 19 to 51+ years) or exceed (e.g., 1,440 for males 11 to 18 years) 1 mg/day. Daily intakes of high consumer males 19 to 50 years and 51+ years could be 1,090 and 1,060 µg folate, respectively. These values are not consistent with the maximum intake limit of 1 mg folate/day. Therefore, the agency cannot authorize a fortification scheme that would produce them.

The agency recognizes that breakfast cereals, unlike breads and other cereal-grain products, are generally consumed only once/day by most adults. Thus, consuming a single daily serving of a highly fortified breakfast cereal is different than consuming multiple daily servings of highly fortified cereal-grain products. However, some consumers such as teenagers may consume multiple servings/day of breakfast cereals, and children may consume breakfast cereals as snacks. Because of increased intakes that might be achieved through such eating patterns, the agency considered the option of proposing that fortification of all breakfast cereals be limited to 100 µg/serving (Table 7). With this option, estimated intakes would remain below 1 mg by all population groups, even if cereal-grain products are fortified with 140 µg folic acid/100 g, and supplements of 400 µg folic acid/unit are available.

FDA recognizes that this proposed action will have the effect of requiring the reformulation of a small number of breakfast cereals. It is not the agency's desire to have such an effect, but it appears to be unavoidable given the current state of the record. The agency is prepared to reconsider this approach if interested persons submit comments that provide data or other information that show that folate consumption can be kept within safe limits with breakfast cereals fortified to 400 µg/serving.

The agency also recognizes that some may find an inequity in the agency's treatment of dietary supplements, with respect to which the agency is proposing to allow continued marketing of a 400 µg folic acid supplement, as compared to its treatment of breakfast cereals, with respect to which it is proposing to establish a 100 µg/serving limit for folic acid. FDA tentatively finds that this approach is appropriate because supplements tend to be used to supplement the diet for specific purposes, while breakfast cereals are

eaten more generally as part of the usual diet. However, the agency requests comment on this matter. While commenters should feel free to suggest alternate approaches, including other combinations of options, such comments will be most useful if they explain how the suggested approach will ensure that total dietary intake of folate will remain within safe limits.

The agency recognizes that its proposal to fortify cereal-grains products at 140 µg/100 g, to allow for fortification of breakfast cereals at 100 µg/serving, and to retain the current limitations for use of folic acid in supplements (i.e., 400 µg folic acid/unit), present a dilemma in that by limiting fortification to levels that provide safe intakes for the general population, the estimated daily folate intake by "low consumers" among women of childbearing age may not reach the PHS recommended levels of 400 µg/day without changes in their food selection practices. However, the proposed fortification levels will mean that, under FDA's estimate, "low consumers" among women of childbearing age will consume 230 to 250 µg/day (Table 4, Option 7). These values represent an increase of 80 to 100 µg over current daily intakes. Significantly, several studies have found that dietary intakes of 250 µg or more daily are associated with a reduced risk of NTD's. Moreover, these levels are also close to intake levels estimated to be sufficient to saturate body tissue stores of folate (Ref. 14). The increased intake of 80 to 100 µg/day is also consistent with the opinion of one Folic Acid Subcommittee member that increases of about 100 µg/day above current intakes could provide protective effects. The agency also notes that intakes of 230 to 250 µg/day are minimum intakes for women of childbearing age, and that most women will have intakes above this level, with some estimated to be close to 800 µg/day. Thus, the agency tentatively finds that even though "low consumers" may not achieve the 400 µg/day recommended by PHS, on balance, particularly in light of the potential effects of higher levels of fortification on the nontarget population, the proposed fortification scheme will produce acceptable results.

Moreover, the agency explained above why it believes that its estimates may underrepresent folate intakes. The agency also noted that its estimates did not factor in any effect that the presence of health claims on food labels will have on food selection choices of women of childbearing age. The agency expects that the availability of health claims on cereal-grain products fortified at the level proposed will result in increased consumption of such products and hence increased folate intake, beyond that that would occur without a health claim. Thus, the availability of a health claim on cereal-grain products fortified at the level proposed and on other sources of dietary folate could lead to food choices that could result in adequate folate intakes even by "low consumer" women of childbearing age.

The agency has tentatively concluded that by providing for moderate increases in folate intakes through fortification and by then providing point-of-purchase information of foods that are good sources of folate on the relationship of adequate folate intake and reduction in risk of NTD's, women of childbearing age will have considerable flexibility in making their dietary choices (including use of supplements) to achieve the PHS recommended intake. This flexibility will also be available to persons who need to or who may wish to limit their folate intakes, and who would find it much more difficult to do so if higher folate levels were used in cereal-grain products, whose use in the diet is difficult to avoid or to significantly reduce.

FDA also calculated examples of likely individual intakes from fortified foods using various levels of fortification (Tables 6A and 6B). For example, a woman who made food choices from the "low" range of the USDA Food Guide Pyramid and who consumed 5 servings/day of cereal-grain products fortified at 140 µg/100 g and ate 1 bowl of cereal containing 100 µg of folic acid would consume about 320 µg of folic acid (i.e., 80 percent of the RDI) from these sources alone (Table 6A). Addition of a serving or two of vegetables, or of a serving of fruit, could lead to a folate intake above 500 µg/day, well in excess of the PHS recommended level of 400 µg of folate/day.

However, if cereal-grain products were fortified at 350 µg/100 g, and the dietary choices indicated above were made, a "low consumer" would obtain 610 µg folic acid daily (153 percent of the RDI) from these sources alone (Table 6A). The agency notes, however, that if cereal-grain products are fortified at the level of 350 µg folic acid/100 g, "high" consumers could reach intakes of folic acid of more than 1,000 µg/day from bread, noodle, rice, and pasta products alone (Table 6B). Additional consumption of breakfast cereals, fruits, vegetables, and a dietary supplement by "high consumers" could result in daily intakes of about 2.5 mg, significantly above the agency's proposed safe upper limit of daily intake of 1 mg.

In summary, FDA has tentatively concluded that its overriding responsibility is to establish a safe range of intakes for all population groups, to maximize folate intakes of the target population within this safe range, and to ensure the safe use of health claims. However, given the dilemma of trying to increase intakes of women of childbearing age while ensuring that intakes by "high consumers" across all segments of the U.S. population are safe, and given the uncertainties in the available data, FDA asks for comment on the appropriateness of its approach and of other options, including higher and lower levels of fortification. In this regard, FDA will carefully consider any data that it receives on the issue of fortification level and target foods and will make any appropriate adjustments based on the review of the data it receives.

The agency also requests comments on several other possibilities for fortification. Specifically, the agency is requesting comments on:

(1) Whether cereal-grain products might be fortified at a lower level (e.g., 70 µg/100 g), thus leaving a greater margin of safety for consumers of supplements and highly fortified cereals and greater flexibility in amounts of folic acid that might be permitted in other foods;

(2) Whether both dietary supplements and breakfast cereals should be limited to the same but lower level (e.g., 100 or 200 µg folic acid/unit or/serving);

(3) Whether, in a food supply that includes a wide range of fortified cereal-grain products, an additional caution statement should be required for all products fortified at 100 percent of the RDI (i.e., 400 µg folic acid/unit or/serving), given that consumption of multiple servings/day of such products (e.g., more than two) will result in daily folate intakes well above 1 mg; and whether a higher level of fortification (e.g., 350 µg/100 g) is more appropriate than the level that FDA is proposing (140 µg/100g).

The agency also requests data on the safety of fortification options for children. In examining the intakes of children, who are among the high consumers of breakfast cereals and dietary supplements, the agency is specifically requesting comments on whether long term, continuous intakes of free folic acid by children at levels of three to four times their RDI's present safety concerns, and if so, what those concerns are. The agency notes that when intake of folate by children increases markedly (e.g., by several multiples of their RDI's), the majority of the increased intake will likely appear

in the blood stream as unmetabolized folic acid. In this regard, the agency calls attention to its estimates that among children 1 to 3 and 4 to 10 years, high consumers could ingest 810 to 1,220 µg folate/day if cereal-grain products were fortified at 140 µg/100 g and if all breakfast cereals were fortified at 400 µg/serving.

Several comments (Ref. 59) suggested that higher folate fortification could be safely implemented if simultaneous fortification with vitamin B_{12} (cobalamin) at a level of 1 mg is also required. These comments are based on assumptions that the greatest potential for adverse effects with high folate intake is its masking of the anemia of vitamin B_{12} deficiency, with continued progression of neurologic damage, and that provision of oral vitamin B_{12} in sufficiently high levels will negate this concern. FDA is aware that doses of about 1 mg/day of vitamin B_{12} (500 times the RDI for this vitamin) without intrinsic factor (i.e., without the protein factor necessary for the absorption of vitamin B_{12}, and the factor whose lack causes pernicious anemia) have provided adequate treatment for some persons with pernicious anemia (Ref. 129). However, Hathcock and Troendle (Ref. 129), in a recent editorial, note that regardless of the widespread availability of oral vitamin B_{12} preparations, patients with pernicious anemia or others at risk of vitamin B_{12} deficiency should be diagnosed, treated, and monitored by a physician.

Several experts at the CDC's recent meeting on surveillance for adverse effects of increased intakes of folate (Ref. 59) commented on the suggestion that high doses of vitamin B_{12} be added to foods and supplements fortified with folic acid to reduce the potential for adverse effects in persons with vitamin B_{12} deficiency. One expert noted that vitamin B_{12} may be converted into analogs, some of which may have antivitamin B_{12} activity, in the presence of certain other nutrients (e.g., vitamin C, thiamin, iron), and that attempts to fortify with vitamin B_{12} would require a demonstration that the vitamin B_{12} added with folic acid remained biologically active and safe.

At this time, FDA is not proposing to include the addition of vitamin B_{12} to foods fortified with folic acid. FDA requests comments, specifically data, on the appropriateness, potential effectiveness, and safety of use of simultaneous fortification with high levels of vitamin B_{12} for the purpose of possibly minimizing the adverse effects of increased folic acid intakes. FDA will consider such comments in arriving at a final rule in this matter. FDA is proposing in separate documents published elsewhere in this issue of the **Federal Register** that standardized enriched cereal-grain products be fortified with folic acid at the level of 140 µg folic acid/100 g, that breakfast cereals be allowed to include up to 100 µg/serving, and that dietary supplements be allowed to contain up to 400 µg folic acid/daily dose when labeled without reference to age or physiologic state. While the agency believes that fortification at either 70 µg or 140 µg folic acid/100 g is safe, it is proposing to require 140 µg/100 g as the folic acid fortification level because this level will provide a better opportunity for a larger portion of the target population to achieve significantly increased folate intakes.

The results of FDA's analysis of food fortification options show that fortification of the U.S. food supply alone cannot increase daily intakes of folate for all women of childbearing age to 400 µg/day if current dietary patterns are continued without increasing the potential for adverse effects in nontarget segments of the population. Apparently some women (i.e., "low consumers") in the target population eat such small amounts of the staple foods that are candidates for fortification that no matter how high the fortification levels are set, the added folic acid would not reach them. The inability of fortification alone to increase the intakes of all target women to 400 µg/day was recognized by a number of experts who consulted with the Folic Acid Subcommittee at its November 23 and 24, 1992 meeting.

VI. Proposed Requirements for Health Claims

A. Relationship Between Folate and NTD's

The 1990 amendments required FDA to evaluate the topic of folic acid and NTD's with respect to its appropriateness for a health claim. The term "folic acid" is the name given to the parent compound of the folate vitamin forms, whereas the term "folates" is used as a descriptor for the entire group of folate vitamin forms and includes both folic acid and the folylpolyglutamates found in foods. In reviewing the scientific evidence on the relationship between folate and NTD's, the agency noted that some studies reported effects of use of supplements of folic acid in combination with intakes of food folates, while other studies reported effects of dietary intakes of food folates alone. Based on its review of these studies, the agency has tentatively concluded that the diet/disease relationship is more correctly expressed as "folate and neural tube defects" rather than as "folic acid and neural tube defects".

Therefore, FDA is proposing in § 101.79 to authorize health claims on labels or in labeling of foods in conventional form or dietary supplements on the relationship between folate and NTD's. Proposed paragraph § 101.79(a)(1) defines the disease or health-related condition that is the subject of the claim. NTD's are rare but serious birth defects that can result in infant mortality or serious disability. The birth defects anencephaly and spina bifida are the most common forms of NTD's and account for about 90 percent of these defects. These defects result from failure of closure of the covering of the brain or spinal cord during early embryonic development. Because the neural tube forms and closes during early pregnancy, the defect may occur before a woman realizes that she is pregnant.

Proposed § 101.79(a)(2) describes the effect of folate intake on the risk of NTD's. FDA's tentative conclusion based on its review of the totality of the scientific evidence and its resolution of safety issues, as reflected in this section of the regulation, is that the available data show that folic acid alone may reduce the risk of recurrence of NTD's when given at high levels (i.e., 4 mg (4000 µg)/day or 10 times the RDI) to women at high risk of such a recurrence. Additionally, based on a synthesis of information from several observational studies that reported use of multivitamins containing 0 to 1,000 µg of folic acid, the PHS, including FDA, concluded that folic acid intake at levels of 0.4 mg (400 µg or 100 percent of the RDI)/day may reduce the risk of occurrence of NTD's (Ref. 11). PHS also stated that a reasonable estimate of the expected reduction in the United States is 50 percent.

B. Significance of the Relationship

Proposed § 101.79(b)(1) summarizes the significance of appropriate folate intake relative to reduction in risk of NTD's in the general U.S. population and within the total dietary context. This paragraph recognizes that reduction in adverse pregnancy outcomes, such as birth defects, is an important public health goal. Because most NTD's occur in women without a history of such outcomes, interest in reducing the risk of first occurrences has been very high.

In the United States, about 2,500 cases of NTD's occur among about 4 million annual births (i.e., in approximately 6 of 10,000 live births). The majority of NTD's are isolated defects and

apparently are produced by a number of factors (Ref. 12). The single greatest risk factor is a personal history of a pregnancy affected with an NTD (Ref. 12). However, about 90 percent of infants with an NTD are born to women who do not have a family history of these defects (Ref. 12).

Proposed § 101.79(b)(2) identifies populations at risk for NTD's. NTD's have been reported to vary with a wide range of factors including genetics, geography, socioeconomic status, maternal birth cohort, month of conception, race, nutrition, and maternal health including maternal age and reproductive history (56 FR 60610). Women with a close relative (i.e., sibling, niece, nephew) with an NTD, with insulin-dependent diabetes mellitus, and with seizure disorders who are being treated with valproic acid or carbamazepine are at significantly increased risk compared with women without these characteristics (Ref. 20). Rates for NTD's also vary within the United States, with lower rates observed on the west coast than on the east coast (56 FR 60610). Recent data from State-based birth defects surveillance systems show declining trends for NTD's in the United States for about the last 30 years (Ref. 18).

In proposed § 101.79(b)(3), FDA notes that PHS (Ref. 11) estimated that if all women of childbearing age in the United States who are capable of becoming pregnant consumed 0.4 mg of folic acid daily throughout their childbearing years, there would be about a 50 percent reduction in the number of infants born with NTD's (i.e., a reduction from about 2,500 annually to about 1,250 annually). The protective effect of about 0.4 to 1 mg of folic acid daily, measured by the reduction in incidence of occurrence of NTD's, has ranged from none to substantial (Refs. 5, 6, 9, and 26). Thus, PHS stated that a reasonable estimate of the expected reduction in the United States is 50 percent (Ref. 11).

C. General Requirements

The agency is proposing in § 101.79(c)(1) to require that to bear a health claim on the relationship between folate and NTD's, foods must meet the general requirements for health claims in § 101.14 (published in the Federal Register of January 6, 1993 (58 FR 2478), except for the requirement in § 101.14(d)(2)(vii) that the food be "high" in the subject nutrient.

Folate is ubiquitously distributed among many foods in the U.S. food supply. While a number of foods (e.g., some legumes, okra, broccoli, spinach, turnip greens, asparagus, Brussels sprouts, endive, lentils) contain more than 80 µg of folate/serving, the great majority of foods contain folate at lower levels. For example, oranges, grapefruit, many berries, cabbage, lettuce, corn, cauliflower, peas, many vegetable juices, beets, and parsnips contain folate at levels of 40 to 80 µg/serving (Ref. 129).

The agency is concerned that if it required (in accord with § 101.14(d)(2)(vii)) that the food contain 20 percent of the RDI for folate (i.e., 80 µg) or more/reference amount customarily consumed, many good food sources of folate would not be able to qualify to bear a health claim without fortification. The current dietary guidance recommendations of five or more servings of fruits and vegetables/day, and six or more servings of grain products/day, if followed, would likely result in daily intakes of folates of 0.4 mg or more. Thus, use of a qualifying criterion consistent with that used to define a "good" source of folate provides for an amount that allows a wide variety of fruits, vegetables, and grain products to qualify and is consistent with current dietary guidelines for general dietary patterns. Because health claims on foods in conventional food form are required to be made within the context of a daily diet, and because FDA has proposed a similar requirement for health claims for dietary supplements, it seems contrary to the intent of the 1990 amendments to set requirements that would essentially limit a health claim to fortified foods or dietary supplements and to a relatively few fruits and vegetables. Accordingly, FDA is proposing in § 101.79(c)(1) and (c)(2)(ii) that foods may bear a folic acid health claim if they contain 10 percent or more of the RDI for folic acid/reference amount customarily consumed (i.e., must meet the definition for a "good source" claim in § 101.54). (Ref. 129).

The general requirements for health claims in § 101.14, among other things, prohibit a health claim if any of the specified disqualifying nutrient levels are exceeded. This requirement ensures that folic acid/NTD health claims will not appear on foods that contain amounts of fat, saturated fat, cholesterol, or sodium that may increase the risk from the total diet of a disease or health-related condition. A thorough discussion of the criteria for identifying risk nutrients and the levels of these nutrients allowed in foods that bear health claims is found in the preamble to the final rule on general principles for health claims (58 FR 2478).

D. Specific Requirements

1. Relationship Statement

In § 101.79(c)(2), the agency is proposing to require that the claim on the relationship of folate and NTD's state that women who are capable of becoming pregnant and who consume adequate folate daily may reduce their risk of having a pregnancy affected by spina bifida or other NTD's.

The agency is proposing to require that the claim specifically relate adequate intake of folate during the childbearing years to reduced risk of NTD's (proposed § 101.79(c)(2)(i)(A)). This proposed action is consistent with observational data (Refs. 6, 8, and 26) showing that adequate intake of folate during the childbearing years may reduce the risk of occurrence of such birth defects.

The agency considered the use of synonyms for "folate" and the need to aid consumers in understanding this nutrient. The agency, therefore, has provided, in proposed § 101.79(2)(i)(B), for the use of synonyms and for additional description of this term through use of phrases such as "folate," "folic acid," "folacin," "folate, a B vitamin," "folic acid, a B vitamin," or "folacin, a B vitamin." The terms "folate" and "folacin" are generic descriptors for compounds that have nutritional properties and chemical structures similar to those of folic acid (Ref. NAS). The terms "folate" and "folacin" are allowable synonyms under § 101.9 and proposed § 101.36. The term "folic acid" is specifically used in the PHS recommendation (Ref. 11), and by allowing use of this term, the PHS recommendation can be quoted directly on the label, if all other requirements for the health claim are met. The use of the descriptive term, "a B vitamin," in conjunction with "folate," "folacin," or "folic acid," is commonly used in lay information for consumers and may be useful for consumers in indicating the nutritive role of folate.

The agency considered whether women might be confused or not understand the term "neural tube defect" and has provided in proposed § 101.79(c)(2)(i)(C) for some qualification of this term through use of phrases such as "the birth defect spina bifida," "the birth defects spina bifida and anencephaly," "spina bifida and anencephaly, birth defects of the brain or spinal cord." Although a phrase like "reduce the risk of serious birth defects" might be simpler, the agency is concerned that if a claim were to state in general terms that "folic acid may reduce the risk of serious birth defects," women would be misled into believing

that folic acid would reduce their risk of other serious birth defects, and that they might consequently fail to consider other risk factors for birth defects (e.g., use of alcohol, drugs).

The agency is proposing to allow, as one option, reference to simply "the birth defect spina bifida" because that is the most common NTD in the United States for which some protective effect of folate has been demonstrated (Refs. 5, 6, 7, and 26). However, because the protective effect of folate has been shown for both spina bifida and anencephaly, both terms may be used. The agency considers that the optional use of the descriptive phrase, "birth defects of the brain or spinal cord" could be useful to consumers in better understanding the nature of the NTD and in differentiating this birth defect from others such as heart defects.

2. Multifactorial Nature

In § 101.79(c)(2)(i)(D), FDA is proposing to require that the claim contain a statement that NTD's are multifactorial in origin. The general requirements for health claims for foods in conventional food form (§ 101.14), which FDA has proposed to apply to health claims for substances in dietary supplements, provide that where factors other than dietary intake of the substance affect the relationship between the substance and disease or health-related condition, FDA may require that such factors be addressed in the health claim.

NTD's have many causes, some of which are not related to folate status. The single greatest risk factor currently recognized, as stated above, is a personal history of an NTD defect-affected pregnancy.

3. Prevalence

In § 101.79(c)(2)(i)(E), the agency is proposing to require that the health claim provide information that NTD's, while not of high prevalence in the United States are very serious birth defects. Because the affected population is few in number and not readily identifiable, FDA is proposing to require such information to prevent women from being misled into believing that NTD's are very common birth defects, or that, lacking a personal or family history of such defects, their risk of having a pregnancy affected with such a birth defect is very high. The prevalence of NTD's in the United States is currently about 6/10,000 live births, or about 2,500 cases/year. In addition, there may be no effect of periconceptional use of folic acid in areas of low prevalence or in areas where other factors are contributing to an increased prevalence. Such a statement is consistent with scientific evidence that shows that in an area of low prevalence of NTD's in the United States, women who consumed folate from multivitamins or fortified cereals did not have a lower risk of having an NTD-affected pregnancy than did women who did not (Ref. 7).

Examples of the statements that the agency is proposing to require are "Such birth defects, while not widespread, are very serious." or "* * * birth defects * * * that, while not widespread, are very serious."

4. Reduction in Risk

In § 101.79(c)(2)(i)(F), the agency is proposing to require that the claim contain a statement that some but not all women may benefit from adequate intakes of folic acid. Such a statement is consistent with estimates provided with the findings in the PHS recommendation that about half of NTD's (about 1,250 annually) could be prevented if all women of childbearing age in the United States who are capable of becoming pregnant consumed 0.4 mg of folic acid daily throughout their childbearing years. Such a statement is necessary to prevent the claim from misleading women to believe that use of folic acid will prevent all occurrences of NTD's.

The agency is also proposing in this section that the claim not attribute any specific degree of reduction in risk of NTD's to maintaining an adequate folate intake throughout the childbearing years.

5. Safe Upper Limit of Intake

As discussed above, a comment received following the November 23 and 24, 1993 Folic Acid Subcommittee meeting suggested that any health claims related to folic acid and NTD's should be balanced by a warning statement that increased intakes of folate may increase the frequency of irreversible neurologic damage from vitamin B_{12} deficiency, and that among African-American and Hispanic females, folic acid fortification or supplementation is likely to do more harm than good. The agency recognizes that for some groups in the population (see safety discussion above), there may be certain risks attendant upon increased consumption of folic acid. At the present time, the potential adverse effect that has been most extensively documented is that of the activity of increased intakes of folate in masking the anemia of vitamin B_{12} deficiency while irreversible neurologic damage progresses.

In recognition of comments and safety concerns discussed above, FDA, in § 101.79(c)(2)(F), is proposing to require a statement on both fortified foods in conventional food form and on dietary supplements that contain more than 25 percent of the RDI (i.e., more than 100 µg/reference amount customarily consumed or, for supplements, per unit) about the maximum safe daily limit for folate consumption. Such a statement is necessary to prevent the claim from being misleading regarding potential risks from excessive intakes. As stated above, the safe intake limit is 1 mg/day. A fortified food that contains more than 100 µg/serving contributes more than 25 percent of the RDI and more than 10 percent of the daily limit. Consumption of such foods should be monitored by the consumer, so that they will not be consistently or significantly exceeding the daily limit. An example of the statement FDA is proposing to require is: "Folate consumption should be limited to 250 percent of the DV (i.e., to 1,000 µg per day)."

The agency is not proposing to require that this statement be included in claims on the relatively small number of conventional foods that contain more than 100 µg of folic acid without fortification (e.g., dark green leafy vegetables, certain legumes). The agency believes that there is no need for the consumer to monitor intakes of these foods because their folate content consists of reduced pteroylpolyglutamates whose bioavailability is generally considered lower than that of the folic acid (i.e., pteroylmonoglutamate) added as a fortificant to foods.

6. Limitation on the Claim

In § 101.79(c)(2)(i)(H), the agency is proposing that a health claim not state that a specified amount of folate is more effective in reducing the risk of NTD's than a lower amount (e.g., 100 µg). This proposed requirement is consistent with data showing that reduction in risk of NTD's has been associated with general dietary improvement (which is assumed to increase folate intake by unspecified amounts).

7. Identifying Sources of Folate

In § 101.79(c)(2)(ii)(B), the agency is proposing to require that health claims relating folate and NTD's identify sources of folate by stating that adequate amounts of folate may be obtained by making specific dietary choices of folate-rich foods, as well as through use of dietary supplements or fortified breakfast cereals. Several studies have shown that among women with a prior NTD-affected pregnancy who improved their poor diets to diets with adequate intakes of all nutrients in a subsequent

pregnancy, there was a 50 percent reduction in recurrence of NTD's (Ref. 9). In addition, several studies have shown that among nonusers of supplements, significant gradients (i.e., trends) in reduction in risk of NTD's are associated with increased intakes of folate and other nutrients (Refs. 8 and 26). One study has shown that among nonsupplement users, diets providing more than 100 µg/day of folate are associated with reduced risk of NTD's (Ref. 6). Thus, the agency has tentatively concluded that claims that fail to reveal that adequate amounts of folate can be obtained through attention to dietary choices would be misleading.

Examples of the statements that the agency is proposing to require to assist women in making dietary choices are: "Women * * * should choose well-balanced diets that include 2 to 4 servings per day of fruits (including citrus fruits and juices), 3 to 5 servings of vegetables (including dark green leafy vegetables and legumes), 6 to 11 servings of enriched grain products (such as breads, rice, and pasta) and fortified cereals throughout their childbearing years. Such diets provide many essential minerals and vitamins, including folate. Women who do not eat well-balanced diets or who may be concerned about their diets may choose to obtain folate from dietary supplements;" or "Adequate amounts of folate, a B vitamin, can be obtained from diets rich in fruits, including citrus fruits and juices, vegetables, including dark green leafy vegetables and legumes, enriched grain products, including breads, rice, and pasta, fortified cereals, or from a dietary supplement;" or "Adequate amounts of folate, a B vitamin, can be obtained from diets rich in fruits, dark green leafy vegetables and legumes, enriched grain products, fortified cereals, or from a dietary supplement."

8. Nutrient Availability

Benefits of folate intake from food in conventional food form and from dietary supplements can only be obtained if the folate is available for metabolism by the body. As discussed above, the bioavailability of folates in foods ranges from approximately 25 to 75 percent, depending upon a variety of factors that are incompletely understood (Ref. 114). The majority of food folates occur as reduced folylpolyglutamates and must be cleaved by intestinal conjugase before absorption. Folate utilization may be reduced under conditions that inhibit conjugase activity and by natural conjugase inhibitors found in certain foods (Ref. 114). However, there are not enough data on factors in specific foods or components of foods that affect folate bioavailability for FDA to determine conditions under which a health claim for folate in foods would be misleading because the folate was not assimilable. On the other hand, crystalline folic acid is generally considered to have a bioavailability greater than that of food folates because it is in the monoglutamate form and does not have to be cleaved by intestinal conjugases (Ref. 114).

A dietary supplement that contains folate that does not disintegrate and dissolve clearly does not provide the nutrient in an assimilable form. Thus, a claim for such a dietary supplement would be misleading because the supplement would not provide the nutrient that is the subject of the health claim.

Dietary supplements can be formulated in a manner that prevents rapid dissolution and disintegration, thereby preventing subsequent absorption of the nutrients they contain. Accordingly, FDA is proposing in § 101.79(c)(2)(ii)(C) to require that dietary supplements that contain folate and that bear a health claim meet the United States Pharmacopeia (U.S.P.) standards for disintegration and dissolution.

However, when U.S.P. standards do not exist, the agency recognizes the need for an alternative method of establishing the bioavailability of the nutrients in dietary supplements under the conditions of use stated on the product label. FDA is proposing that demonstrations of bioavailability in human or animal studies when conducted under the conditions of use stated on the product label (i.e., fed as an intact tablet, not crushed) will fulfill this requirement. Thus, proposed § 101.79(c)(2)(ii)(C) provides that if there are no applicable U.S.P. standards, the folate in the dietary supplement shall be shown to be bioavailable under the conditions of use stated on the product label.

9. Prohibition of Claims on Fortified Products That Contain More than 100 Percent of the RDI for Vitamins A and D

The agency is aware that folate is often combined with other nutrients, particularly vitamins and minerals, in dietary supplement formulations. In light of the expectation that the presence of a health claim on the label of such products is likely to encourage the intake of these products, FDA is concerned that some consumers may try to increase their folate intake through the use of multiple doses of fortified products or vitamin supplements. The agency is concerned that for some fortified products that contain both folate and vitamin A or vitamin D, consumers could be exposed to excessive vitamin A or vitamin D intakes in their attempts to obtain increased amounts of folate.

It is widely recognized that vitamin A in excessive amounts is teratogenic (Ref. 15). A high incidence (greater than 20 percent) of spontaneous abortions and of birth defects, including malformations of the cranium, face, heart, thymus, and central nervous system, have been observed in the fetuses of women ingesting therapeutic doses (0.5 to 1.5 mg/kilogram) of 13-*cis*-retinoic acid (isotretinoin) during the first trimester of pregnancy, and large daily doses of retinyl esters or retinol (≥ 6,000 retinol equivalents or 20,000 International Units (IU)) may cause similar abnormalities (Ref. 15).

Vitamin D is potentially toxic, with effects of excessive intakes including hypercalcemia and hypercalciuria (Ref. 15). Although the toxic level of vitamin D has not been established for all ages, consumption of as little as 1,800 IU of cholecalciferol/day has been associated with signs of hypervitaminosis in young children (Ref. 15). The toxic level of vitamin D may in some cases be only 5 times the RDA (Ref. 15).

The 1991 CDC recommendation for increased intake of folate by women with a history of an NTD-affected pregnancy warned against overconsumption of multivitamins because of the potential for excessive intakes of vitamins A and D from such preparations (Ref. 11). In addition, recent recommendations in Canada for women of childbearing age regarding folic acid and NTD's included consideration of the teratogenicity of high levels of vitamin A (Ref. 56).

Based on this information, FDA tentatively concludes that to prevent folate health claims from inadvertently encouraging excessive intakes of vitamins A and D, it is necessary to prohibit the health claim for folate on supplement formulations that contain more than 100 percent of the RDI of vitamin A and vitamin D. Therefore, FDA is proposing in § 101.79(c)(2)(iii) that the health claim be prohibited on foods in conventional food form and on dietary supplements that contain more than 100 percent of the RDI for vitamin A or vitamin D. Educational materials regarding increasing intake of folate to reduce the risk of NTD's should include precautionary information about excessive intakes of vitamins A and D.

10. Nutrition Labeling—Requirement that Nutrition Labeling Be Provided for Foods and Supplements Bearing Health Claims

FDA is proposing to require in § 101.79(c)(2)(iv) that the nutrition label of any food that bears a health claim on folate and neural tube defects include information about the folate content of the food. This proposed requirement is consistent with § 101.9(c)(8)(ii), which states that the declaration of vitamins and minerals on the nutrition label shall include any of the vitamins and minerals listed in § 101.9(c)(8)(iv) when a claim is made about them, and with proposed § 101.36(b)(3), which requires a listing of any vitamin or mineral listed in § 101.9(c)(8)(iv) that is present in the product. FDA also sets forth in proposed § 101.79(c)(2)(iv) how the information on folate content is to be presented. The agency is doing so in the interest of clarity.

E. Optional Health Claim Information

Consistent with general requirements for health claims (21 CFR 101.14), FDA is proposing optional information that may be included in the health claim. The agency is proposing to permit manufacturers, in addition to including the fact that risk of NTD's is multifactorial, to specifically identify other risk factors for NTD's (§ 101.79(c)(3)(i)). Although not identified in the regulation, specific examples of other risk factors might include a personal history of such a defect, maternal diabetes mellitus, use of the antiepileptic drug valproic acid, maternal febrile illness, or a close relative (sibling, niece, nephew) with an NTD.

The agency is also proposing to permit the claim to include statements from paragraphs (a) and (b) of § 101.79 that summarize the relationship between folic acid and NTD's and the significance of the relationship (proposed § 101.79(c)(3)(ii)). The proposed provision excludes from these permitted statements information specifically prohibited from the claim. This exception is consistent with the proposed prohibition in § 101.79(c)(i)(F) against statements that give specific degrees of reduction in risk of NTD's.

Proposed paragraph (a)(2) on the relationship between folic acid and NTD's includes a statement that a reasonable estimate of the expected reduction in NTD's incidence in the United States is 50 percent. This 50 percent estimate is based on observational studies that showed reductions in risk from none to substantial (Ref. 11), is population-based, and does not apply to the reduction in risk for an individual. FDA believes that while the statement is appropriate in the context in which it is presented in paragraph (a)(2), it could be misleading to consumers in food label as part of a health claim. It is unlikely that a label statement about a 50 percent reduction in incidence could be properly qualified on a food label so that it would not incorrectly imply a 50 percent reduction in risk to the individual.

Available data clearly show that the single greatest risk factor for an NTD-affected pregnancy is a personal history of the defect. The agency tentatively concludes that a statement that women with a history of an NTD pregnancy should consult their physicians or health care providers before becoming pregnant would encourage them to obtain medical guidance and thus decrease their possibility of a recurrence of another NTD-affected pregnancy. The agency is proposing to permit such a statement as a part of the health claim (proposed § 101.79(c)(3)(iii)).

The agency is also proposing to include as optional information in the health claim a statement that the target folate intake goal is the RDI level of 400 µg/day and not to require that this information be included as part of the claim (proposed § 101.79(i)(3)(iv)).

Following the April 1993 Folic Acid Subcommittee meeting, an expert speaker commented that the 400 µg/day dose of folic acid was an artificial goal. The expert noted that there are no data demonstrating that 400 µg/day is the required amount, and that there are data to suggest that this amount is more than is required to reduce the risk of NTD's. The expert noted further that if 400 µg/day were required, little or no impact (with respect to reduction in risk of NTD's) should have been seen in those studies that looked at diet because daily dietary intakes of folate are generally below 400 µg. Studies by Werler et al.,(Ref. 26), Bower and Stanley (Ref. 8), Laurence (Ref. 9), and Milunsky et al. (Ref. 6), all have suggested, however, that there are pronounced effects from levels of dietary folate lower than 400 µg/day.

In its January 6, 1993 final rule, the agency noted that a number of studies have shown significant effects of diet in reducing risk of NTD's. The findings of these studies are listed in Table 3. These studies suggest the potential efficacy of lower doses of folate in reducing the risk of NTD's, and the benefits of overall dietary improvement for women during their childbearing years. Some studies (Refs. 6 and 26) have shown significant risk reduction at folate intakes well below 400 µg/day.

However, because the PHS recommends a 400 µg/day intake, the RDI is 400 µg, and the Folic Acid Subcommittee supported the 400 µg/day intake goal, the agency believes that it may be helpful to some consumers if the health claim for folate were to include information that the RDI of 400 µg/day is the target intake goal.

F. Model Health Claims

FDA is providing examples of model claims that meet the proposed requirements in proposed § 101.79(d). The agency is including these model claims to assist manufacturers in formulating an appropriate claim.

G. Effective Date

FDA is proposing that for fortified foods, the regulation authorizing a health claim on folate and NTD's become effective on the effective date for the amendment to the folic acid food additive regulation. In the final rule on a health claim for folic acid and NTD's on January 6, 1993 (58 FR 2606), FDA noted that it could not allow a health claim on this topic area until issues of safe use could be resolved. FDA, at that time, was concerned that a health claim could motivate manufacturers to increase fortification of foods in order to qualify for health claims, and consumers could also increase use of foods bearing a health claim. Taken together, these two events could result in potentially high intakes of folic acid for which safety was an issue.

In this document, FDA has tentatively concluded that by amending its food additive regulation for folic acid, it can ensure that a health claim for folate and NTD's can be safely implemented. However, because the safe use of the health claim is based on the concurrent implementation of the amendment to the folic acid food additive regulation, FDA is proposing that the health claim regulation not become effective until the food additive amendment is effective.

On the other hand, because of the significance of the information provided in the health claim, and because of the absence of an issue about the safe level of use of folate in foods that naturally contain this nutrient and in dietary supplements, FDA is proposing that § 101.79 would become effective for these foods 30 days after the date of publication of this final rule.

VII. Comments

Interested persons may, on or before December 13, 1993, submit to the Dockets Management Branch (address above) written comments regarding this

proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

During the comment period on this and the two related documents on folic acid, the agency intends to convene the Folic Acid Subcommittee and the Food Advisory Committee for a discussion of the issues raised in the documents. FDA also intends to request comments from the experts who participated in its November 23 and 24, 1992, meeting of its Folic Acid Subcommittee. The agency will make these comments and the views of the committees available for public review and comment as part of this rulemaking immediately after the Advisory Committee meeting is held. In addition, FDA will endeavor to have copies of the transcripts of the Folic Acid Subcommittee and Food Advisory Committee meetings available as quickly as possible as well.

VIII. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. Because the agency is taking three actions involving folic acid, and the net effect of these actions is likely to increase the usage of folic acid, one environmental assessment has been prepared which considers all three agency actions.

IX. Economic Impact

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

The agency is proposing to authorize health claims for folate and NTD's. Because no products are currently making health claims concerning folate and NTD's, the proposed rule will not adversely affect any labels currently being used. FDA believes that there are no costs associated with the proposed rule.

The allowance of a health claim for folate and NTD's will, to the extent that folate health claims appear on products and to the extent that consumers read and understand that health claim, result in an unquantifiable benefit in terms of the education of consumers about the relationship between folate, diet, health, and NTD's. Folate health claims may result in increased demand for products containing this nutrient. An increase in consumption of products containing folate is likely to result in health benefits in terms of fewer NTD's. However, FDA is not able to estimate the number of products that will bear health claims or the effect that folate health claims will have on consumer demand for products containing folic acid. FDA requests comment on these factors.

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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under the 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 continues to read as follows:

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

§ 101.71 [Amended]

2. Section 101.71 *Health claims: claims not authorized* is amended by removing paragraph (c) and by redesignating paragraphs (d) through (f) as (c) through (e), respectively.

3. New § 101.79 is added to subpart E to read as follows:

§ 101.79 Health claims: folate and neural tube defects.

(a) *Relationship between folate and neural tube defects*—(1) *Definition.* Neural tube defects are serious birth defects of the brain or spinal cord that can result in infant mortality or serious disability. The birth defects anencephaly and spina bifida are the most common forms of neural tube defects and account for about 90 percent of these defects. These defects result from failure of closure of the covering of the brain or spinal cord during early embryonic development. Because the neural tube forms and closes during early pregnancy, the defect may occur before a woman realizes that she is pregnant.

(2) *Relationship.* The available data show that diets adequate in folate may reduce the risk of neural tube defects. The strongest evidence for this relationship comes from an intervention study by the Medical Research Council of the United Kingdom that showed that women at risk of recurrence of a neural tube defect pregnancy who consumed a supplement containing 4 milligrams (mg) (4,000 micrograms (μg)) folic acid daily had a reduced risk of having a child with a neural tube defect. (Products that contain this level of folic acid are drugs.) In addition, based on its review of a Hungarian intervention trial that used a multivitamin and multimineral preparation containing 800 μg (0.8 mg) of folic acid, and its review of the observational studies that reported use of multivitamins containing 0 to 1,000 μg of folic acid, the Food and Drug Administration concluded that most of these studies had results consistent with the conclusion that folate, at levels attainable in usual diets, may reduce the risk of neural tube defects.

(b) *Significance of folate*—(1) *Public health concern.* Neural tube defects occur in approximately 0.6 of 1,000 live births in the United States (i.e., about 2,500 cases among 4 million live births annually). Neural tube defects are believed to be caused by many factors. The single greatest risk factor for a neural tube defect-affected pregnancy is a personal or family history of a pregnancy affected with a such a defect. However, about 90 percent of infants with a neural tube defect are born to women who do not have a family history of these defects. The available evidence shows that diets adequate in folate may reduce the risk of neural tube defects but not of other birth defects.

(2) *Populations at risk.* Prevalence rates for neural tube defects have been reported to vary with a wide range of factors, including genetics, geography, socioeconomic status, maternal birth cohort, month of conception, race, nutrition, and maternal health, including maternal age and reproductive history. Women with a close relative (i.e., sibling, niece, nephew) with a neural tube defect, those with insulin-dependent diabetes mellitus, and women with seizure disorders who are being treated with valproic acid or carbamazepine are at significantly increased risk compared with women without these characteristics. Rates for neural tube defects vary within the United States, with lower rates observed on the west coast than on the east coast.

(3) *Those who may benefit.* Based on a synthesis of the results of several observational studies, the Public Health Service has estimated that about 50 percent of neural tube defect-affected pregnancies in the United States (e.g., about 1,250) may be averted annually if all women consume adequate amounts of folate daily (i.e., 0.4 mg) throughout their childbearing years.

(c) *Requirements.* The label or labeling of food in conventional food form or dietary supplements may contain a folate/neural tube defect health claim provided that:

(1) *General requirements.* The health claim for a food or supplement meets all of the general requirements of § 101.14 for health claims, except that a food or dietary supplement may qualify to bear the health claim if it meets the definition of the term "good source."

(2) *Specific requirements*—(i) *Nature of the claim*—(A) *Relationship.* A health claim that women who are capable of becoming pregnant and who consume adequate amounts of folate daily during their childbearing years may reduce their risk of having a pregnancy affected by spina bifida or other neural tube defects may be made on the label or labeling of foods in conventional food form or of dietary supplements provided that:

(B) *Specifying the nutrient.* In specifying the nutrient, the claim shall use the terms "folate," "folic acid," "folacin," "folate, a B vitamin," "folic acid, a B vitamin," or "folacin, a B vitamin."

(C) *Specifying the condition.* In specifying the health-related condition, the claim shall identify the birth defects as "neural tube defects," "birth defects, spina bifida, or anencephaly," "birth defects of the brain or spinal cord anencephaly or spina bifida," or "spina bifida or anencephaly, birth defects of the brain or spinal cord;"

(D) *Multifactorial nature.* The claim shall state that neural tube defects have many causes and shall not imply that folate intake is the only recognized risk factor for neural tube defects.

(E) *Prevalence.* In specifying the prevalence of neural tube defects among women in the general population, the claim shall state that such birth defects "which, while not widespread, are extremely significant" or "* * * birth defects * * * that, while not widespread, are extremely significant."

(F) *Reduction in risk.* The claim shall not attribute any specific degree of reduction in risk of neural tube defects, including mention of the Public Health Service estimate that 50 percent of neural tube defects may be averted annually, to maintaining an adequate folate intake throughout the childbearing years. The claim shall state that some women may reduce their risk of a neural tube defect pregnancy by maintaining adequate intakes of folic acid during their childbearing years.

(G) *Safe upper limit of daily intake.* Claims on fortified foods in conventional form and on dietary supplements that contain more than 25 percent of the RDI for folate (100 µg per serving or per unit) shall state that 1 mg folate per day is the safe upper limit of intake (e.g., "Folate consumption should be limited to 1,000 µg per day from all sources").

(H) *The claim.* The claim shall not state that a specified amount of folate (e.g., 400 µg in a dietary supplement) is more effective in reducing the risk of neural tube defects than a lower amount (e.g., 100 µg in a breakfast cereal or from diets rich in fruits and vegetables).

(ii) *Nature of the food—(A) Requirements.* The food or supplement shall meet or exceed the requirements for a good source of folate as defined in § 101.54;

(B) *Diets adequate in folate.* The claim shall identify diets adequate in folate by using phrases such as "* * * diets that include 2 to 4 servings per day of fruits) including citrus fruits and juices), 3 to 5 servings of vegetables (including dark green leafy vegetables and legumes), 6 to 11 servings of enriched grain products (such as breads, rice, and pasta) and fortified cereals. Such diets provide many essential minerals and vitamins, including folate. Women who do not eat well-balanced diets or who may be concerned about their diets may choose to obtain folate from dietary supplements."; or "Adequate amounts of folate, a B vitamin, can be obtained from diets rich in fruits, including citrus fruits and juices, vegetables, including dark green leafy vegetables and legumes, enriched grain products, including breads, rice, and pasta, fortified cereals, or a dietary supplement."; or "Adequate amounts of folate, a B vitamin, can be obtained from diets rich in fruits, dark green leafy vegetables and legumes, enriched grain products, fortified cereals, or from dietary supplements."

(C) *Dietary supplements.* Dietary supplements shall meet the United States Pharmacopeia (U.S.P.) standards for disintegration and dissolution, except that if there are no applicable U.S.P. standards, the folate in the dietary supplement shall be shown to be bioavailable under the conditions of use stated on the product label.

(iii) *Limitation.* The claim shall not be made on foods in conventional food form or dietary supplements that contain more than 100 percent of the RDI for vitamin A as retinol or preformed vitamin A or vitamin D.

(iv) *Nutrition labeling.* The nutrition label shall include information about the amount of folate in the food. This information shall be declared after the declaration for iron if only the levels of vitamin A, vitamin C, calcium, and iron are provided, or in accordance with § 101.9 (c)(8) and (c)(9) if other optional vitamins or minerals are declared.

(3) *Optional information—(i) Risk factors.* The claim may specifically identify risk factors for neural tube defects;

(ii) *Relationship between folate and neural tube defects.* The claim may include statements from paragraphs (a) and (b) of this section that summarize the relationship between folate and neural tube defects and the significance of the relationship except for information specifically prohibited from the claim.

(iii) *Personal history of a neural tube defect-affected pregnancy.* The claim may state that women with a history of a neural tube defect pregnancy should consult their physicians or health care providers before becoming pregnant.

(iv) *Daily value.* The claim may identify the daily value level of 400 µg of folate per day as the target intake goal.

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

(1) *Example 1.* Women who consume adequate amounts of folate, a B vitamin, daily throughout their childbearing years may reduce their risk of having a child with a neural tube birth defect. Such birth defects, while not widespread, are very serious. They can have many causes. Adequate amounts of folate can be obtained from diets rich in fruits, dark green leafy vegetables and legumes, enriched grain products, fortified cereals, or a supplement. Folate consumption should be limited to 1,000 µg per day from all sources.

(2) *Example 2.* Women who consume adequate amounts of folate daily throughout their childbearing years may reduce their risk of having a child with a birth defect of the brain and spinal cord. Such birth defects, while not widespread, are very serious. They can have many causes. Adequate amounts of folate, a B vitamin, can be obtained from diets rich in fruits, dark green leafy vegetables and legumes, enriched grain products, fortified cereals, or a supplement. Women who have had a child with a spinal cord birth defect should consult a physician before becoming pregnant. Folate consumption should be limited to 1,000 µg per day from all sources.

(3) *Example 3.* Women who take steps to ensure that their folate intake is adequate throughout their childbearing years may reduce their risk of having a child with a neural tube defect. Such birth defects, while not widespread, are very serious. They can have many causes. Adequate amounts of folate, a B vitamin, can be obtained from diets rich in citrus fruits and juices, dark green leafy vegetables and legumes, enriched grain products such as breads, rice, and pasta, fortified cereal, or a supplement. Folate consumption should be limited to 1,000 µg per day from all sources.

(4) *Example 4.* Women who take steps to ensure that their folate intake is at least 400 µg daily throughout their childbearing years may reduce their risk of having a child with spina bifida or anencephaly, birth defects of the brain or spinal cord that, while not widespread, are very serious. These birth defects can have many causes. Adequate amounts of folate, a B vitamin, can be obtained from diets rich in fruits, including citrus fruits and juices, vegetables, including dark green leafy vegetables and legumes, enriched grain products, including breads, rice, and pasta, fortified cereals, or from a supplement. Women who have had a pregnancy affected with a neural tube defect should consult a physician before becoming pregnant. Folate consumption should be limited to 1,000 µg per day from all sources.

(5) *Example 5.* Some women who consume the Daily Value of folate (400 µg) throughout their childbearing years may reduce their risk of having a child affected with spina bifida or anencephaly, birth defects of the brain or spinal cord that, while not widespread, are very serious. These birth defects can have many causes. Women of childbearing age should choose well-balanced diets that include 2 to 4 servings per day of fruits (including citrus fruits and juices), 3 to 5 servings of vegetables (including dark green leafy vegetables and legumes), 6 to 11 servings of enriched grain products (such as breads, rice, and pasta) or fortified cereals throughout their childbearing years. Such diets provide many essential minerals and vitamins, including folate. Women who may be concerned about their diets may choose to obtain folate from a supplement.

Folate consumption should be limited to 1,000 µg per day from all sources.

(e) *Effective date.* For fortified foods, this regulation is effective on the date the food additive regulation on the use of folic acid that was proposed on October 14, 1993, becomes effective.

Dated: October 1, 1993.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

Note: The following tables are to the Preamble and will not appear in the annual Code of Federal Regulations.

TABLE 1.—FOLIC ACID AND NEURAL TUBE DEFECTS: COMPOSITION OF SUPPLEMENTS USED IN INTERVENTION TRIALS

Composition (vitamins and minerals)	Smithells et al., 1983 (ref. 2)	Medical research council trial (ref. 4)	Hungarian trial (ref. 24)	National research Council (ref. 123)	
				25 to 50 y	
				Female	Pregnant
Vitamin A—IU	4,000	4,000	6,000	2,660[1]	2,660[1]
Vitamin D—IU	400	400	500	200	400
Thiamin (B_1)—mg	1.5	1.5	1.6	1.1	1.5
Riboflavin (B_2)—mg	1.5	1.5	1.8	1.3	1.6
Pyridoxine (B_6)—mg	1.0	1	2.6	1.6	2.2
Vitamin C—mg	40	40	100	60	70
Niacin (Niacinamide)—mg	15	15	19	15	17
Vitamin E—TE	0	0	15	8	8
Folic acid—mg	0.36	4 or 0 (see below)	0.8	0.18	0.40
Vitamin B_{12}—µg	0	0	4	2.0	2.2
Vitamin K—µg	0	0	0	65	65
Ca. pantothenate—mg	0	0	10	4 to 7[2].	
Biotin—mg	0	0	0.2	0.03 to 0.10[3].	
Mg—mg	0	0	100	280	320
Ca—mg	480 mg calcium	240 mg dicalcium	125 mg Ca	800	1,200
P—mg	phosphate	phosphate	125 mg P	800	1,200
				15	30
Fe—mg	75.6 mg Fe	120 mg ferrous sulfate	60 mg Fe	12	15
Zn—mg	0	0	7.5	1.5 to 3.0[3].	
Cu—mg	0	0	1	2.0 to 5.0[3].	
Mn—mg	0	0	1.		
I—µg	0	0	0.		
Se—µg	0	0	0.		
	Treatments: Vitamins (as above) or unsupplemented.	Treatments: (A) Ca+Fe + 4 mg folate, (B) Ca+Fe+vitamins + 4 mg folate, (C) Ca+Fe, (D) Ca+Fe+vitamins without folate.	Treatments: Multivitamin & multimineral supplement or placebo. Placebo contained Zn, Cu, and Mn as above + vitamin C (as calcium ascorbate, 7.3 mg) and lactose.		

[1] 800 RE; 1 IU vitamin A = 0.30 retinol equivalents (RE)
[2] ESADDI (adults)
[3] TE: 1 mg alpha tocopherol = alpha tocopherol equivalent (TE)

TABLE 2.—FOLIC ACID AND NEURAL TUBE DEFECTS: DEFINITIONS OF SUPPLEMENTS WHOSE USE WAS REPORTED IN OBSERVATIONAL STUDIES

Study	Mulinare et al., 1988 (ref. 5)	Mills et al., 1989 (ref. 7)	Milunsky et al., 1989 (ref. 6)	Werler et al., 1993 (ref. 26)
Years covered.	1968 to 1980	1985 to 1987	1984 to 1987	1988 to 1991

TABLE 2.—FOLIC ACID AND NEURAL TUBE DEFECTS: DEFINITIONS OF SUPPLEMENTS WHOSE USE WAS REPORTED IN OBSERVATIONAL STUDIES—Continued

Study	Mulinare et al., 1988 (ref. 5)	Mills et al., 1989 (ref. 7)	Milunsky et al., 1989 (ref. 6)	Werler et al., 1993 (ref. 26)
Outcome	Use of vitamins was protective ...	Use of vitamins or fortified cereals was not protective..	Use of vitamins was protective	Use of vitamins was protective.
Definition of multivitamins.	Multivitamins or prenatal vitamins were not defined; compositions were unknown. Based on years of data collection (1968 to 1980), supplements could have contained 0 to 800 µg of folate/unit.	Multivitamins were defined as supplements containing the U.S. RDA of at least 4 vitamins. No further specification of compositions.	Multivitamins were not defined. A substantial majority of the preparations whose use was reported contained vitamins A, C, D, and/or E. Based on a random sample of 150 multivitamin users, daily doses of folate ranged from 100 to 1,000 µg with distribution as follows: 100 µg, 17%; 300 µg, 23%; 400 µg, 22%; 1,000 µg, 45%.	Multivitamin was defined as any supplement containing at least two vitamins, one of which was water-soluble. Most common dose of folate, 400 µg/unit.

TABLE 3.—FOLIC ACID AND NEURAL TUBE DEFECTS: REPORTED ASSOCIATIONS BETWEEN MATERNAL DIET AND RISK OF NEURAL TUBE DEFECTS

Study	Dietary observations
Laurence, 1983 (Ref. 9)	This intervention study of dietary guidance found that improvement in women's diets from "poor" to "good" led to a 50 percent reduction in recurrence of neural tube defects in a subsequent pregnancy in women at high risk of this complication. "Poor" diets were defined as diets considered to be deficient in first-class protein, usually no fruits or vegetables, and generally with excessive amounts of carbohydrates. "Good" diets were defined as diets providing good intakes of all essential foods, including protein, no excessive amounts of refined carbohydrates, sweets, and soft drinks.
Bower and Stanley, 1989 (Ref. 8) ...	The study found an association between increasing intakes of dietary folate and decreased risk of occurrence of neural tube defects. Protective effects were also observed for increasing intakes of dietary fiber, calcium, vitamin C, and carotene, markers usually associated with consumption of fruits and vegetables.
Milunsky et al., 1989 (Ref. 6)	Dietary folate intake was calculated from the diet portion of the study questionnaire for those women who were not taking a multivitamin supplement. Nonusers of supplements who had dietary folate intakes greater than 100 µg/day had a 50 percent lower incidence of neural tube defects than did nonusers of supplements whose diets provided less than 100 µg of folate per day.
Werler et al., 1993 (Ref. 26)	For nonusers of supplements, there was a statistically significant trend of decreasing risk of occurrence of a neural tube defect for quintiles of dietary folate intake. Percent reductions in risk for daily dietary folate intakes of 0.253 to 0.310 mg, 0.311 to 0.391 mg, and 0.392 to 2.195 mg were 30, 40, and 40 percent, respectively.

TABLE 4.—FORTIFICATION SCENARIOS—ESTIMATED FOLATE INTAKES FOR LOW AND HIGH CONSUMERS[1,2,3,4]

[Goal for the target population: Intakes of low consumers should be as high as possible. Goal for nontarget population groups: Intakes of high consumers should be within the safe range (≤ 1 mg/day).]

Option	Target population				Non-target population											
	F 11 to 18 y		F 19 to 50 y		MF 1 to 3 y		MF 4 to 10 y		M 11 to 18 y		M 19 to 50 y		M 51 + y		F 51 + y	
	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
1. Current intakes: foods only	140	420	110	370	120	350	160	430	200	560	160	510	170	480	140	400
2. Current intakes: foods + supplements (400 µg/unit)	150	700	150	700	150	470	190	720	220	810	190	760	200	750	170	710
3. Grains[2] + 0.070 mg/100 g	180	490	160	430	140	390	190	490	260	600	210	560	220	540	180	450
4. Grains + 0.140 mg/100 g	220	550	190	470	160	420	230	530	310	670	260	640	260	600	210	510
5. Grains + 0.350 mg/100 g	350	770	290	680	220	520	350	730	460	980	400	920	370	810	290	690
6. Grains + 0.070 mg/100 g + supplements (400 µg)	190	730	190	750	190	500	240	780	270	900	240	830	260	790	210	770
7. Grains + 0.140 mg/100 g + supplements (400 µg)	240	770	240	790	220	540	270	830	330	950	300	880	300	840	250	800
8. Grains + 0.350 mg/100 g + supplements (400 µg)	370	970	360	970	300	670	390	1,030	490	1,180	460	1,100	420	1,050	350	980
9. Grains, juices[3], & dairy[4] + 0.070 mg/100 g	280	1,110	210	810	370	1,110	400	1,110	440	1,320	280	1,080	310	940	240	810
10 Grains, juices, & dairy + 0.140 mg/100 g	420	1,840	280	1,260	590	1,960	630	1,790	660	2,250	380	1,690	400	1,540	330	1,280
11. Grains, juices, & dairy + 0.350 µg/100 g	830	4,050	480	2,650	1,230	4,550	1,300	4,020	1,230	5,040	650	3,550	670	3,240	580	2,670
12. Grains, juices, & dairy + 0.070 µg/100 g + supplements (400 µg)	320	1,250	280	1,070	450	1,250	480	1,310	470	1,480	330	1,250	360	1,140	310	1,100

[1] Data bases:

A. 1987 to 1988 U.S. Department of Agriculture's Nationwide Food Consumption Survey (NFCS);

B. Only individuals with 3 days of data were selected;

C. This survey apparently underreports food intake. For example, for women 19 to 50 years, the average reported energy intake is only about 70 percent of the current average requirement (1-day data = 70 percent; 3-day average = 67 percent). See text for additional details.

[2] Assumptions used for fortification scenarios—Cereal-grain products: Fortification levels of 0.07, 0.14, and 0.35 mg folic acid/100 g were applied to the following dry enriched cereal-grain products: wheat flours; corn grits; corn meals; farinas; rice; macaroni; spaghetti; and noodles.

For breakfast cereals: The majority of breakfast cereals are currently fortified with 100 µg of folic acid/serving (i.e., 25 percent per serving of the RDI for folic acid). Other breakfast cereals contain 35 to 45 percent of the RDI for folic acid, while a limited number contain 100 percent of the RDIs for many vitamins and minerals, including folic acid. The data base provided brand-specific consumption data for these cereals. For about the fifty top-selling breakfast cereals, in instances in which the current folic acid content of the cereal (identified from a review of food labels in a local supermarket) differed from the values used in the USDA data base, the USDA data base values were updated with the more recent values. Thus, values assigned to these breakfast cereals were generally reflective of what is currently in the marketplace. Note: This correction was not applied to cooked breakfast cereals because of the lack of brand-specific information.

[3] Assumptions used for fortification scenarios—Juices: Fortification levels as above were applied to fruit juices (e.g., orange, grapefruit, lemon, pineapple, apple, grape, prune, peach, etc.).

[4] Assumptions used for fortification scenarios—Dairy products: Fortification levels as above were applied to the following dairy products: fluid cow's milk, reconstituted dry milk, condensed, and evaporated milks; and yogurts (Note: codes for "dry milk, not reconstituted" were excluded).

Use of Dietary Supplements:

The following response categories were considered to represent supplements that might contain folic acid: "multivitamin," "multivitamin with iron or other minerals," "other combination of vitamins and minerals," or "other single vitamins/minerals." The following response categories were considered not to represent supplements that might contain folic acid: "combination of vitamin C and iron," "vitamin C", "iron", or "calcium." Currently available adult supplements contain 400 µg folic acid/unit.

A. For persons ≥ 4 years of age: Persons ≥ 4 years who reported consuming supplements that could contain folic acid (e.g., multivitamins, single vitamins) were assigned an intake value of 400 µg/day if they reported consuming supplements "every day" or "almost every day". Persons ≥ 4 years were assigned an intake value of 200 µg of folic acid daily if they indicated that they consumed supplements that might contain folic acid "every so often".

B. For persons 1 to 3 years of age: Persons 1 to 3 years who reported consuming supplements that could contain folic acid (e.g., multivitamins, single vitamins) were assigned an intake value of 200 µg/day if they reported consuming supplements "every day" or "almost every day". Persons 1 to 3 years were assigned an intake value of 100 µg of folic acid daily if they indicated that they consumed supplements that might contain folic acid "every so often".

TABLE 5.—PROS AND CONS OF FORTIFICATION OPTIONS IN WHICH CEREAL-GRAIN PRODUCTS ARE FORTIFIED WITH 70, 140, OR 350 µg FOLIC ACID/100 g[1]

Options for fortification	Pros	Cons	Comments
Fortify cereal-grain products with 70 □g folic acid/100 g (Estimates #3, 6: Table 4) Estimates of results: —10 µg/serving of breakfast cereal made with fortified wheat flour or corn meal —20 µg/slice of fortified bread —30 µg/serving of noodles made with fortified flour	Low consumers in target population could consume 160 to 180 µg or more of folic acid per day (approximately 35 to 45% increase over current intakes) without supplement use (Est. #3). With supplement use (Est. #6), low consumers in target population could consume 190 µg or more folic acid per day (approximately 30% increase over current intakes). Intakes by high consumers in subgroups of adults 51+ years could be 450 to 540 µg/day without supplement use (Est. #3) and 770 to 790 µg/day with supplement use (Est. #6).	For low consumers, intakes of folate do not reach the PHS-recommended level of 400 µg/day.	Use of 1 mg/day as the maximum safe upper limit of intake is consistent with PHS recommendation. Intakes by high consumers in adult population subgroups would remain within this limit with supplement use, even when considering likely underreporting biases (underreporting of food intake and underestimation of folate content of foods).
Fortify cereal-grain products with 140 µg folic acid/100 g (Estimates #4, 7: Table 4) Estimates of results: —20 µg/serving of breakfast cereal made with fortified wheat flour or corn meal —40 µg/slice of fortified bread —60 µg/serving of noodles made with fortified flour	Low consumers in target population could consume 190 to 220 µg or more folic acid per day (approximately 60 to 80% increases over current intakes) without supplement use (Est. #4). With supplement use (Est. #7)), low consumers in target population could consume 240 µg or more folic acid per day (approximately 60% increase over current intakes).	For low consumers, intakes of folate do not reach the PHS-recommended level of 400 µg/day. Folate intakes by high consumers among adults 51+ years could reach 800 to 840 µg/day with supplement use (Est. #7).	With supplement use, daily intakes of high consumers among children 4 to 10 years exceed 800 µg/day. This value is somewhat below the PHS-recommended safe upper limit without taking into account likely underreporting biases regarding food intakes and underestimation of folate content of foods.
Fortify cereal-grain products with 350 µg folic acid/100 g (Estimates #5, 8: Table 4) Estimates of results: —50 µg/serving of breakfast cereal made with fortified wheat flour or corn meal —90 µg/slice of fortified bread —150 µg/serving of noodles made with fortified flour	Low consumers in target population could consume 290 to 350 µg or more of folic acid/day without supplement use (Est. #5). With supplement use, low consumers in target population could consume 360 to 370 µg folate/day (Est. #8).	Daily intakes of folate for all consumers 11 years and older are in the range of 680 to 980 µg without supplement use and 970 to 1,180 µg with supplement use.	With supplement use, daily intakes of high consumers among children 1 to 3 years and 4 to 10 years are 670 µg and 1,030 µg, respectively, without taking into account likely underreporting biases regarding food intakes and underestimation of folate content of foods.

[1] Examples of levels of folate that could be present in typical products (i.e., breads, breakfast cereals and noodles manufactured from enriched flours) are included for reference purposes. Bread: 1 serving=1 slice=50 g; Composition: Approximately 50% flour. Folic acid content: 17.5 µg folic acid/serving with use of flour fortified with 70 µg/100 g and 35 µg folic acid/serving with use of flour fortified with 140 µg folic acid/100 g. Values rounded to 20 and 40 µg, respectively.

TABLE 6A.—EXAMPLES OF LIKELY DAILY INTAKES OF FOLATE FROM FOLIC ACID-FORTIFIED CEREAL-GRAIN PRODUCTS AND OTHER FOODS IF THE USDA FOOD PYRAMID RECOMMENDATIONS WERE FOLLOWED—LOW INTAKES

Examples of effects of fortification of cereal-grain products with folic acid

(A) Daily consumption—low intakes based on the USDA food choice pyramid with fortification of cereral-grains at:

70 µg/100 g	Folic acid µg	140 µg/100 g	Folic acid µg	350 µg/100 g	Folic acid µg
4 srvs breads @ 20 µg/srv	80	4 servs breads @ 40 µg/srv	160	4 srvs breads @ 90 µg/srv	360
1 srv cereal	100	1 srv cereal	100	1 srv cereal	100
1 srv noodles/pasta	30	1 srv noodles/pasta	60	1 srv noodles/pasta	150
1 srv milk	5	1 srv milk	5	1 srv milk	5
1 srv cheese	20	1 srv cheese	20	1 srv cheese	20
1 srv peas	90	1 srv peas	90	1 srv peas	90
1 srv cauliflower	55	1 srv cauliflower	55	1 srv cauliflower	55
1 srv veg. w/o sig. folate	0	1 srv veg. w/o sig. folate	0	1 srv veg. w/o sig. folate	0
1 apple	5	1 apple	5	1 apple	5
1 orange	25	1 orange	25	1 orange	25
2 srvs beef	10	2 srvs beef	10	2 srvs beef	10

TABLE 6A.—EXAMPLES OF LIKELY DAILY INTAKES OF FOLATE FROM FOLIC ACID-FORTIFIED CEREAL-GRAIN PRODUCTS AND OTHER FOODS IF THE USDA FOOD PYRAMID RECOMMENDATIONS WERE FOLLOWED—LOW INTAKES—Continued

Examples of effects of fortification of cereal-grain products with folic acid

(A) Daily consumption—low intakes based on the USDA food choice pyramid with fortification of cereral-grains at:

	70 µg/100 g		140 µg/100 g		350 µg/100 g
	Folic acid µg		Folic acid µg		Folic acid µg
Folate µg/day	420	Folate µg/day	530	Folate µg/day	820
+ 1 supplement µg/day	400	+ 1 supplement µg/day	400	+ 1 supplement µg/day	400
Total µ/day	820	Total µ/day	930	Total µ/day	1,200
Percent of RDI	205	Percent of RDI	233	Percent of RDI	305
Percent of RDI attainable from fortified cereal-grain products 210/400 = 53%.		Percent of RDI attainable from fortified cereal-grain products 320/400 = 80%.		Percent of RDI attainable from fortified cereal-grain products 610/400 = 153%.	

The current USDA food pyramid recommends daily consumption of 6 to 11 servings from the bread, cereal, rice, and pasta group, 2 to 3 servings from the dairy group, 3 to 5 servings of vegetables, 2 to 4 servings of fruit, and 2 to 3 servings from the meat, poultry, fish, dry beans, eggs, and nuts group. The examples above show estimates of average daily intakes of folate that could result if the USDA food pyramid recommendations were followed and cereal-grain products were fortified with folic acid. Most breakfast cereals are currently fortified with 25 percent of the RDI for folate/serving (i.e., 100 µg/serving). One option regarding amendment of the food additive regulation for folic acid could permit fortification of breakfast cereals at levels up to 400 µg/serving. The estimates were calculated to show the effects on intakes with these additional sources of folic acid. The "percent of RDI" estimates use the 1980 RDA for folate of 400 µg.

TABLE 6B. EXAMPLES OF LIKELY DAILY INTAKES OF FOLATE FROM FOLIC ACID-FORTIFIED CEREAL-GRAIN PRODUCTS AND OTHER FOODS IF THE USDA FOOD PYRAMID RECOMMENDATIONS WERE FOLLOWED—HIGH INTAKES

Examples of effects of fortification of cereal-grain products with folic acid

(B) Daily consumption—high intakes based on the USDA food choice pyramid with fortification of cereal-grains at:

	70 µg/100 g		140 µg/100 g		350 µg/100 g
	Folic acid, µg		Folic acid, µg		Folic acid, µg
8 srvs breads @ 20 µg/srv	160	8 srvs breads @ 40 µg/srv	320	8 srvs breads @ 90 µg/srv	720
1 srv cereal	400	1 srv cereal	400	1 srv cereal	400
2 srvs noodles/pasta	60	2 srvs noodles/pasta	120	2 srvs noodles/pasta	300
2 srvs milk	10	2 srvs milk	10	2 srvs milk	10
1 srv cheese	20	1 srv cheese	20	1 srv cheese	20
1 srv peas	90	1 srv peas	90	1 srv peas	90
1 srv cauliflower	55	1 srv cauliflower	55	1 srv cauliflower	55
1 srv spinach	50	1 srv spinach	50	1 srv spinach	50
1 srv cabbage	15	1 srv cabbage	15	1 srv cabbage	15
1 srv broccoli	180	1 srv broccoli	180	1 srv broccoli	180
1 apple	5	1 apple	5	1 apple	5
3 oranges	75	3 oranges	75	3 oranges	75
2 srvs beef	10	2 srvs beef	10	2 srvs beef	10
2 srvs beans	140	2 srvs beans	140	2 srvs beans	140
Folate µg/day	1,270	Folate µg/day	1,490	Folate µg/day	2,070
+ 1 supplement µg/day	400	+ 1 supplement µg/day	400	+ 1 supplement µg/day	400
Total µg/day	1,670	Total µg/day	1,890	Total µg/day	2,470
Percent of RDI	418	Percent of RDI	473	Percent of RDI	618
Percent of RDI attainable from fortified cereal-grain products 620/400 = 155%.		Percent of RDI attainable from fortified cereal-grain products 840/400 = 210%.		Percent of RDI attainable from fortified cereal-grain products 1,420/400 = 355%.	

The current USDA food pyramid recommends daily consumption of 6 to 11 servings from the bread, cereal, rice, and pasta group, 2 to 3 servings from the dairy group, 3 to 5 servings of vegetables, 2 to 4 servings of fruit, and 2 to 3 servings from the meat, poultry, fish, dry beans, eggs, and nuts group. The examples above show estimates of average daily intakes of folate that could result if the USDA food pyramid recommendations were followed and cereal-grain products were fortified with folic acid. Most breakfast cereals are currently fortified with 25 percent of the RDI for folate/serving (i.e., 100 µg/serving). One option regarding amendment of the food additive regulation for folic acid could permit fortification of breakfast cereals at levels up to 400 µg/serving. The estimates above were calculated to show the effects on intakes with these additional sources of folic acid. The "percent of RDI" estimates use the 1980 RDA for folate of 400 µg.

TABLE 7.—ESTIMATES OF FOLATE INTAKES IF ALL BREAKFAST CEREALS WERE FORTIFIED WITH FOLIC ACID AT 100 µg/srv OR 400 µg/srv: LOW AND HIGH CONSUMERS [1]

Options [1]	Target population				Non-target population											
	F 11 to 18 y		F 19 to 50 y		MF 1 to 3 y		MF 4 to 10 y		M 11 to 18 y		M 19 to 50 y		M 51+ y		F 51+ y	
	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
1. Current intakes: foods only	140	420	110	370	120	350	160	430	200	560	160	510	170	480	140	400
If cereals=100 µg/srv	130	390	110	360	120	340	160	410	200	500	160	460	170	420	140	370
If cereals=400 µg/srv	140	880	120	640	170	690	230	830	210	1,090	160	810	180	750	150	620
2. Current intakes: foods + supplements(400 µg/unit)	150	700	150	700	150	470	190	720	220	810	190	760	200	750	170	710
If cereals=100 µg/srv	150	670	150	690	150	460	190	690	220	760	190	730	200	720	170	700
If cereals=400 µg/srv	170	1,040	160	910	250	770	350	1,040	270	1,340	190	970	230	1,000	190	850
3. Grains [2]+0.070 mg/100 g	180	490	160	420	140	390	190	490	260	600	210	560	220	540	180	450
If cereals=100 µg/srv	170	440	150	400	140	360	200	470	260	570	210	520	220	490	170	420
If cereals=400 µg/srv	190	930	160	690	200	710	270	860	280	1,150	220	850	230	800	190	660
4. Grains + 0.140 mg/100 g	220	550	190	470	160	420	230	530	310	670	260	640	260	600	210	510
If cereals=100 µg/srv	220	530	190	460	160	390	230	510	310	650	260	610	260	540	210	470
If cereals=400 µg/srv	240	970	200	730	230	790	310	900	340	1,210	270	930	290	840	220	690
5. Grains + 0.350 mg/100 g	350	770	290	680	220	520	330	730	460	980	400	920	370	810	290	690
If cereals=100 µg/srv	340	760	290	660	220	500	330	690	450	950	400	890	360	790	290	630
If cereals=400 µg/srv	380	1,220	300	890	280	870	430	1,060	520	1,390	420	1,190	410	1,040	320	840
6. Grains + 0.070 mg/100 g + supplements (400 µg)	190	730	190	750	190	500	240	780	270	900	240	830	260	790	210	770
If cereals=100 µg/srv	190	720	190	740	190	480	240	740	270	840	240	790	250	780	210	750
If cereals=400 µg/srv	230	1,090	210	950	270	790	390	1,080	320	1,390	240	1,030	280	1,040	230	900
7. Grains + 0.140 mg/100 g + supplements (400 µg)	240	770	240	790	220	540	270	830	330	950	300	880	300	840	250	800
If cereals=100 µg/srv	250	760	230	780	220	520	280	800	330	910	300	850	300	830	250	790
If cereals=400 µg/srv	270	1,140	250	980	300	810	440	1,120	380	1,440	310	1,090	330	1,060	270	950
8. Grains + 0.350 mg/100 g + supplements (400 µg)	370	970	360	970	300	670	390	1,030	490	1,180	460	1,100	420	1,050	350	980
If cereals=100 µg/srv	370	950	350	950	300	660	390	1,010	490	1,140	460	1,060	420	1,040	340	950
If cereals=400 µg/srv	430	1,300	380	1,130	380	890	550	1,280	570	1,640	480	1,290	470	1,230	390	1,090

[1] Values in the top lines of rows 1 through 8 above are the same as those shown in Table 4 and are estimates of intakes based on current consumption patterns and current marketing practices (lines 1 and 2) and estimates of intakes based on current consumption patterns and current marketing practices with cereal-grain products fortified as described above (lines 3 through 8). Examination of additional options included calculation of intakes if all breakfast cereals were fortified at 100 µg or 400 µg folic acid per serving. All such estimates were based on current consumption patterns.

[2] Fortification of cereal-grain products: Fortification levels of 70, 140, and 350 mneg folic acid/100 g were applied to dry cereal-grain products as described in Table 4.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 93N-0289]

RIN 0905-AD96

Food Labeling; Health Claims for Dietary Supplements

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

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

DATES: Written comments by December 13, 1993.

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

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

SUPPLEMENTARY INFORMATION:

I. Background

A. Passage of 1990 Amendments

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) (Pub. L. 101-535), which amended the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorized the Secretary of Health and Human Services (the Secretary), and FDA by delegation, to issue regulations authorizing health claims on the label or labeling of foods. Under these new health claim provisions, a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under sections 403(r)(3) and (r)(5)(D) of the act (21 U.S.C. 343(r)(3) and (r)(5)(D)).

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

B. The 1991 Health Claims Proposals

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

Based on its review of the available scientific information, FDA tentatively found that four relationships were supported, and it proposed to allow health claims on food labels for calcium and osteoporosis, sodium and hypertension, fat and cardiovascular disease, and fat and cancer. FDA conditionally concluded that two other claims—fiber and heart disease and fiber and cancer—required additional information. Additionally, because sufficient scientific information was lacking, FDA proposed not to permit claims for four nutrient disease relationships: Folic acid and neural tube defects; antioxidant vitamins and cancer; zinc and immune function in the elderly; and *omega*-3 fatty acids and heart disease.

C. The Dietary Supplement Act of 1992

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

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

On January 6, 1993, FDA published final rules on the general requirements for health claims on the labels and in the labeling of foods in conventional food form (58 FR 2478) and final rules authorizing health claims on seven nutrient/disease relationships (calcium and osteoporosis; fat and cancer; saturated fat and cholesterol and CHD; fiber-containing grain products, fruits, and vegetables and cancer; fruits, vegetables and grain products that contain fiber and risk of CHD; sodium and hypertension; and fruits and vegetables and cancer).

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

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

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

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

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

F. Provisions of the Proposed Rule—Regulation Amended

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

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

II. Dietary Fiber and Cancer

A. The 1991 Proposed Findings

In the **Federal Register** of November 27, 1991 (56 FR 60566), FDA published a proposal on the use of a health claim regarding the relationship of dietary fiber and cancer. After reviewing the available scientific evidence, it tentatively found that there was not a sufficient basis to authorize the use of health claims regarding the relationship of dietary fiber and a reduction in the risk of cancer on the labels or in the labeling of foods, including dietary supplements. The agency tentatively found that while data supported an association between consumption of fiber-rich plant foods and a reduced risk of cancer, they did not establish a basis on which to find that this effect was attributable to the fiber itself.

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

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

FDA cited several key factors (56 FR 60566 at 60576 and 60577) that formed a basis for its tentative conclusion that the use of a health claim relating the intake of fiber to a reduced risk of cancer was not sufficiently supported by scientific evidence. These factors included: (1) The fact that the prospective epidemiologic studies that exist are few in number and have had mixed results; (2) insufficient data exist to demonstrate that it is the total dietary fiber, or a specific fiber component, that is related to any reduction of cancer risk; (3) the need for better defined measures of dietary fiber and for standardized descriptions of the source, type, and amount of dietary fiber; and (4) a lack of composition data on the fiber content of foods that precluded estimates of dietary intakes of total dietary fiber or fiber components in most human studies (56 FR 60566 at 60577 and 60578).

B. The January 1993 Final Rule

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

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

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

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

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

C. Summary of Comments

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

Two comments requested clarification of the term "without fortification" as used in the final rules. One of these comments also requested clarification that the use of fiber-containing ingredients in bakery products that already contain fiber does not constitute fortification. Another comment stated that in the agency's discussion of dietary fiber in its final rule on mandatory nutrition labeling, it equated "fortification" with "supplementation," a definition that connotes an addition to a fiber source so that the resulting level of fiber in that source exceeds the indigenous level (58 FR 2079 at 2096, January 6, 1993). Therefore, the comment asked FDA to clarify that the combination of multiple grains in a food, each of which contains an indigenous level of fiber, is not fortification as the agency used the term in its final rule.

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

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

D. The Proposal

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

Because a supplement would contain only fiber, and there is no evidence that any specific fiber itself caused the effects that were seen in studies involving fiber-rich fruits, vegetables, and grain products, FDA tentatively finds that an appropriate basis for proposing to authorize a claim on dietary fiber and cancer on dietary supplements does not exist (56 FR 60566 and 58 FR 2537).

III. Dietary Fiber and Cardiovascular Disease

A. The 1991 Proposed Findings

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

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

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

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

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

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

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

B. The January 1993 Final Rule

In the **Federal Register** of January 6, 1993 (58 FR at 2552), FDA published a final rule announcing its decision to authorize a health claim regarding the relationship of diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain dietary fiber (particularly soluble fiber) and a reduced risk of CHD. The agency reviewed numerous authoritative documents, as well as recent research on dietary fiber and CHD risk (58 FR 2552 at 2552 through 2562). In addition, the agency reviewed the comments that it received (58 FR 2552 at 2562 through 2572).

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

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

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

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

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

C. Summary of Comments

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

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

D. The Proposal

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

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

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

IV. Antioxidant Vitamins and Cancer

A. The 1991 Proposed Findings

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

The agency tentatively found that there was no basis to authorize such claims regarding the relationship of antioxidant vitamins and cancer on the labels and in the labeling of foods. The agency found that strong epidemiologic evidence existed that showed that consumption of fruits and vegetables, which tended to contain higher amounts of vitamin C, were associated with reduced risk of cancers in some sites, notably the stomach and gastrointestinal tract. However, the agency also tentatively found that it was not possible to determine from the available data whether the reduced risks of cancer at specific sites were caused by the vitamin C content of the foods, by other components that were present in those foods, or by general dietary patterns that included those foods (56 FR 60624 at 60636). The agency further recognized that consumption of food sources of vitamin E was frequently, but not consistently, associated with lowered risk of cancer at a number of sites. However, the agency tentatively concluded that the data did not demonstrate that vitamin E itself was responsible for this association, and that the data did not permit identification of the other factors that might produce or prevent the effect. In addition, the agency tentatively found that the data were insufficient to determine the amount of vitamin E needed to produce the effect (56 FR 60624 at 60638).

B. The January 1993 Final Rule

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

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

1. Vitamin E

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

2. *Beta*-carotene

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

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

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

3. Vitamin C

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

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

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

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

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

C. Summary of Comments

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

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

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

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

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

D. The Proposal

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

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

V. Zinc and Immune Function in the Elderly

A. The 1991 Proposed Findings

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

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

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

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

B. The January 1993 Final Rule

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

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

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

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

C. Summary of Comments

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

D. The Proposal

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

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

VI. Omega-3 Fatty Acids and Coronary Heart Disease

A. 1991 Proposed Findings

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

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

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

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

B. The January 1993 Final Rule

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

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

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

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

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

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

C. Summary of Comments

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

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

D. The Proposal

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

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

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

VII. The Next Steps

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

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

FDA must consider both the validity of the link between the substance and the disease condition and the safety of the substance, especially when the purpose of the proposed health claim is to encourage intake of substance (in contrast to the claims on fat, for example, which encourage moderation in consumption). Care in reviewing safety is especially important when the claim is made for a substance in a dietary supplement because consumption of dietary supplements, in contrast to most foods in conventional food form, is not self-limiting.

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

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

VIII. FDA's Plan for Completing a Final Rule

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

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

IX. Comments

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

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

X. Economic Impact

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

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

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

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

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

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

XI. Environmental Impact

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

List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

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

PART 101—FOOD LABELING

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

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355, 371); sec. 202(a)(2) of the Dietary Supplement Act (Pub. L. 102–571).

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

§ 101.71 Health claims: claims not authorized.

* * * * *

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

* * * * *

Dated: October 1, 1993.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 136, 137, and 139

[Docket No. 91N–100S]

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

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

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

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

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

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

SUPPLEMENTARY INFORMATION:

I. Background

In September 1992, following an open meeting sponsored by the Centers for Disease Control (CDC) in Atlanta, GA (57 FR 29323) and based on reviews of the relevant scientific data, PHS recommended that all women of childbearing age in the United States consume 0.4 mg (400 µg) of folate daily to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects (Ref. 1). In discussing this recommendation, PHS raised several issues that directly bear on FDA's responsibilities under the Federal Food, Drug, and Cosmetic Act (the act). One of these issues was to identify the best approach for increasing intake of folate by women during their childbearing years. PHS identified several possible approaches by which folate intake by the target population might be increased. These approaches included: (1) Improvement of dietary habits, (2) fortification of the U.S. food supply, and (3) daily use of folate supplements by women throughout their childbearing years. The PHS recommendation also cautioned against the effects of higher intakes of folate. The recommendation stated that a widely recognized adverse effect of high intakes of folate is masking the anemia of vitamin B_{12} deficiency and thus allowing the neurologic damage to progress untreated. PHS said that care should be taken to keep total folate consumption at less than 1 mg (1,000 µg)/day, except under the supervision of a physician (Ref. 1).

After the PHS recommendation was issued, FDA convened a subcommittee on folate of its Food Advisory Committee (hereinafter referred to as the "Folic Acid Subcommittee") to consider some of the issues raised by the recommendation. At a meeting in November 1992, the Folic Acid Subcommittee discussed approaches for ensuring that the folate intakes of women would be increased. It identified several approaches. These included: (1) Development of a fortification scheme such that 90 percent of women of childbearing age could receive at least 400 µg of folate per day from all sources, while preventing excessively high folate intakes by nontarget groups; (2) appropriate labeling of foods, including dietary supplements; and (3) implementation of an educational program directed primarily at women of childbearing age that emphasizes the importance of folate intake before, during, and after conception and its effect on the incidence of neural tube defects. The Folic Acid Subcommittee also recommended that a surveillance and monitoring system be established to provide baseline data on vitamin B_{12} status in subgroups of the population that might potentially be at greatest risk as a result of increased intakes of folate.

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

II. The Proposal

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

FDA is proposing to amend the following standards of identity to require the addition of folic acid: Enriched bread, rolls and buns (§ 136.115 (21 CFR 136.115)); enriched flour (§ 137.165 (21 CFR 137.165)); enriched self-rising flour (§ 137.185 (21 CFR 137.185)); enriched corn grits (§ 137.235 (21 CFR 137.235)); enriched corn meals (§ 137.260 (21 CFR 137.260)); enriched farina (§ 137.305 (21 CFR 137.305)); enriched rice (§ 137.350 (21 CFR 137.350)); enriched macaroni products (§ 139.115 (21 CFR 139.115)); enriched nonfat milk macaroni products (§ 139.122 (21 CFR 139.122)); and enriched noodle products (§ 139.155 (21 CFR 139.155)). FDA notes that the standards of identity for enriched bromated flour (§ 137.160 (21 CFR 137.160)), enriched vegetable macaroni products (§ 139.135 (21 CFR 139.135)), and enriched vegetable noodle products (§ 139.165 (21 CFR 139.165)) cross-reference the standards of identity for enriched flour, enriched macaroni products, and enriched noodle products, respectively, and will thus also be amended by this proposal. FDA also points out that the standard for enriched macaroni products fortified with protein is stayed and thus will not be addressed in this rulemaking.

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

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

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

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

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

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

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

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

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

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

The agency has also tentatively decided that the appropriate fortification level for cereal-grain products is 140 µg/100 g. Based on the results of its analysis, fortification of cereal-grain products with 140 µg/100 g will provide daily intakes for the nontarget population that remain within the recommended safe upper limit of approximately 1 mg/day, while providing increased intakes of folate for women in their childbearing years. The agency notes that with supplement use, 95th percentile intakes by adults 51+ years of age could reach 840 to 860 µg/day if these enriched cereal-grain products are fortified with 140 µg/100 g. While the agency recognizes that this level approaches the recommended safe upper limit and does not take into account likely underreporting biases regarding food intakes and underestimation of folate content of foods, it tentatively concludes that fortification of cereal-grain products with 140 µg/100 g folic acid is the most appropriate fortification level of the three levels analyzed to ensure that folate intakes by the target population will increase. Fortification at a lower level of 70 µg/100 g may not provide sufficient folate levels to that portion of the target population that have lower daily food intakes or that consume minimal amounts of cereal-grain products. For example, folate intake estimates for the 25th percentile of the target population if cereal-grain products were supplemented with 70 µg/100 g of folic acid showed levels of 160 to 180 µg/day without supplement use and 200 µg/day with supplement use.

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

A. Bakery and Wheat Flour Products

1. Enriched Flour

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

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

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

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

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

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

2. Enriched Rolls and Buns

For consistency with the requirements for enriched flour products, FDA is proposing to amend the standards of identity for enriched bread, rolls, and buns in § 136.115 to require that these foods contain 0.43 mg/lb of folic acid. This rate of fortification is proportionally consistent with the fortification rate used for the B vitamins (thiamin, riboflavin, and niacin) when enriched flour is used in making these foods. For example, the levels of thiamin, riboflavin, and niacin in enriched flour (§ 137.165) are 2.9, 1.8, and 24.0 mg/lb, respectively, and in enriched bread (§ 136.115) are 1.8, 1.1, and 15.0 mg/lb, resulting in a ratio of approximately 1.62 to 1. In the case of the level of folic acid, the proposed level for enriched flour is 0.7 mg/lb compared to 0.43 mg/lb for bread, resulting in a ratio 1.63 to 1. The lower level specified for the B vitamins and folic acid content in enriched bread products allows the bread products to be made from the standardized enriched flour without further fortification.

3. Enriched Farina

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

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

B. Corn and Rice Products

1. Enriched Corn Grits

USDA Handbook 8–20 data (Ref. 7) show that corn products, except for corn meals, contain significantly less folate than wheat products, ranging from a low of 0.005 mg/100 g (0.022 mg/lb) in dry corn grits to a high of 0.031 mg/100 g (0.141 mg/lb) in degermed corn meals and 0.057 mg/100 g (0.258 mg/lb) in bolted corn meals. However, because corn products are often used as substitutes for wheat based food products, FDA is proposing to amend § 137.235 to require fortification of enriched corn grits with the same level of folic acid as that proposed for enriched wheat flour products, such that each pound of the food would contain at least 0.7 mg of folic acid. Because there may be losses from the rinsing of corn grits before cooking, FDA is also proposing an upper limit for folic acid fortification of 1.0 mg/lb, which is approximately 50 percent higher than the proposed minimum of 0.7 mg/lb, as it has done for the other B vitamins (thiamin, riboflavin, and niacin) that are required to be present in enriched corn grits.

2. Enriched Corn Meals

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

3. Enriched Rice

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

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

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

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

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

C. Macaroni and Noodle Products

The standards of identity for enriched macaroni products (§ 139.115), enriched nonfat milk macaroni (§ 139.122), and enriched noodle products (§ 139.155), and the cross-referenced standards of identity for enriched vegetable macaroni products (§ 139.135) and enriched vegetable noodle products (§ 139.165), provide for significantly higher levels of nutrient addition than the related flour standards of identity because these products are usually cooked in a large amount of water that is usually discarded after cooking and before consumption of the macaroni and noodle products. FDA is proposing to require addition of folic acid to macaroni and noodle products in the same proportion as it is proposing for use in enriched flour, except that the proposed level (expressed in terms of a range) will be approximately 25 percent higher than the proposed level of folic acid to be added to flour. This 25 percent increase is consistent with that of the other added nutrients (thiamin, riboflavin, niacin, and iron) in the enriched macaroni and noodle products standards compared to those in the standards of identity for flour products. Accordingly, FDA is proposing to require that the enriched macaroni and noodle products contain from 0.9 to 1.2 mg/lb of folic acid.

The agency requests comments on whether the proposed fortification levels discussed for the above products are appropriate. Interested persons who wish to suggest alternative fortification levels should include a rationale for such levels and data to support the suggested levels. Further, the agency requests comments on whether addition of folic acid to these cereal-grain products should be required as proposed or should be optional because increased levels of folate intake present health risks to persons with vitamin B_{12} deficiency.

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

III. Economic Impact

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

A. Options

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

B. Costs

1. Improve Dietary Practices Among Women of Childbearing Age

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

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

Excess folate intake can interfere with the diagnoses of vitamin B_{12} deficiency at levels as low as 0.25 mg per day. There is no scientific consensus on the percentage of diagnoses of vitamin B_{12} deficiency that would be complicated by folate intake at this level. However, the agency has tentatively determined that adverse health effects are not significant until folate intake reaches 1 mg per day. Under this option, folate intake will be below 1 mg per day for all individuals.

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

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

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

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

Folic acid fortification at 0.07 mg/100 g will not raise the folate intake of consumers at risk of vitamin B_{12} deficiency and pernicious anemia to levels greater than 1 mg per day. The

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

Folic acid fortification at 0.35 mg/100 g will raise the folate intake of some consumers at risk of vitamin B_{12} deficiency and pernicious anemia to levels exceeding 1 mg per day. As an example of the costs involved, a simple linear extrapolation of the results of a study that found that between 50 percent and 77 percent of patients with pernicious anemia experienced prolonged hematological remission to a dose of 5 mg of folate per day will be used (Ref. 9).

A delay in the diagnosis of vitamin deficiency can result in severe and potentially irreversible neurologic damage. The most common irreversible consequences of a delay in the diagnosis of vitamin B_{12} deficiency are permanent paresthesia (numbness or tingling) in the hands or feet and ataxia (inability to coordinate voluntary muscular movements). Based on the number of people estimated to be at risk of pernicious anemia, and on a study dealing with the prevalence of permanent paresthesia and ataxia in cases of pernicious anemia initially diagnosed at the stage at which neurologic symptoms are present, consumers may experience health consequences valued at approximately $1.85 billion per year under this level of folic acid fortification (Ref. 10).

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

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

C. Benefits

1. Improve Dietary Practices Among Women of Childbearing Age

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

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

The benefit of this option is a reduction in the incidence of infants born with neural tube defects (NTD's). PHS has estimated that if all women of childbearing age achieved an intake of 0.4 mg folate per day the incidence of NTD's could be reduced by 50 percent.

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

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

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

The birth defects anencephaly and spina bifida are the most common forms of NTD's and account for about 90 percent of these defects. Spina bifida is a serious condition that is associated with a variety of adverse health effects. One study of the effects of spina bifida found that 41 percent of patients born with spina bifida died before their 16th birthday (Ref. 12). Assuming that the estimated number of infant deaths are due primarily to anencephaly, the increase in life expectancy due to the elimination of the estimated number of cases of spina bifida is estimated to be about $323 million. This study also found that 20 percent of patients with spina bifida who did not die before their 16th birthday suffered from mental retardation, 30 percent were wheelchair bound, and 44 percent incontinent (Ref. 12). The estimated benefit from the elimination of these adverse health effects is estimated to be $205 million per year (Ref. 11). This estimate is based on a willingness-to-pay methodology that includes, for example, cost of illness and pain and suffering. Benefit estimates based solely on cost of illness would be significantly lower. Additional adverse health effects from NTD's were also observed but were relatively rare and will not be considered here.

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

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

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

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

D. Conclusion

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

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

IV. Environmental Impact

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

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

prepared which considers all three agency actions.

V. References

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

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

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

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

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

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

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

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

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

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

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

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

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

VI. Comments

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

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

List of Subjects

21 CFR Part 136

Bakery products, Food grades and standards.

21 CFR Part 137

Cereals (food), Food grades and standards.

21 CFR Part 139

Food grades and standards.

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

PART 136—BAKERY PRODUCTS

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

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

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

§ 136.115 Enriched bread, rolls, and buns.

(a) * * *

(1) Each such food contains in each pound 1.8 milligrams of thiamin, 1.1 milligrams of riboflavin, 15 milligrams of niacin, 0.43 milligrams of folic acid, and 12.5 milligrams of iron.

* * * * *

PART 137—CEREAL FLOURS AND RELATED PRODUCTS

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

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

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

§ 137.165 Enriched flour.

* * * * *

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

* * * * *

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

§ 137.185 Enriched self-rising flour.

* * * * *

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

* * * * *

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

§ 137.235 Enriched corn grits.

(a) * * *

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

* * * * *

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

§ 137.260 Enriched corn meals.

(a) * * *

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

* * * * *

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

§ 137.305 Enriched farina.

(a) * * *

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

* * * * *

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

§ 137.350 Enriched rice.

(a) * * *

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

* * * * *

PART 139—MACARONI AND NOODLE PRODUCTS

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

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

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

§ 139.115 Enriched macaroni products.

(a) * * *

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

* * * * *

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

§ 139.122 Enriched nonfat-milk macaroni products.

(a) * * *

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

* * * * *

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

§ 139.155 Enriched noodle products.

(a) * * *

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

* * * * *

Dated: September 13, 1993.

David A. Kessler,

Commissioner of Food and Drugs.

[FR Doc. 93–25030 Filed 10–7–93; 2:51 pm]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. 91N–100F]

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

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

DATES: Written comments by December 13, 1993.

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

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

SUPPLEMENTARY INFORMATION:

I. Background

A. Introduction

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

The 1990 amendments required that FDA evaluate 10 nutrient-disease relationships with respect to their appropriateness for health claims; the topic of folic acid and neural tube defects was among those 10 topics. On November 27, 1991, the agency proposed (56 FR 60610) not to authorize the use of a health claim relating to an association between folic acid [1] and neural tube defects on the label or in labeling of foods, including dietary supplements. The agency tentatively concluded that there was not significant agreement among qualified experts that intakes of folic acid at levels permitted under the food additive regulation would be protective against occurrence of neural tube defects in pregnancies of women in the U.S. population.

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

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