publish the proposal to amend the regulations to provide for the requested use of the health claim in the **Federal Register** within 90 days of the date of filing. The proposal will also announce the availability of the petition for public review.

§ 101.71 Health claims: claims not authorized.

In response to the Nutrition Labeling and Education Act of 1990, FDA has reviewed the evidence on the following topics that Congress specifically asked FDA to evaluate and has concluded that there is no basis for claims about the following:

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

[FR Doc. 91-27151 Filed 11-26-91; 8:45 am]

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21 CFR Part 101

[Docket No. 91N-0098]

RIN 0905-AD03

Food Labeling: Health Claims; Dietary Fiber and Cancer

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing that after reviewing the available evidence, it tentatively finds that a basis does not exist on which to authorize the use on foods, including dietary supplements, of health claims relating to an association between ingestion of dietary fiber and reduction in risk of cancer. While data support an association between consumption of fiber-rich plant foods and reduced risk of cancer, FDA tentatively finds that it cannot attribute this effect to the fiber itself. Therefore, FDA specifically requests comments on this topic. FDA has reviewed the relationship between this dietary component and this disease under the provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments).

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the 1990 amendments.

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: Joyce J. Saltsman, Center for Food Safety and Applied Nutrition (HFF-265), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-485-0316.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Nutrition Labeling and Education Act of 1990

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

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

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

B. Basis for Considering a Claim Relating Dietary Fiber and Cancer

1. Cancer

Cancer accounts for about one of every five deaths and is the second leading cause of death in the United States (DHHS/PHS, 1990). Deaths from cancer numbered more than 475,000 in 1987. The overall economic cost of cancer, including direct health care costs and losses due to morbidity and mortality, was estimated to be $72.5 billion. In addition, the social impact of cancer can be measured in part by potential years of life lost by death before age 65. Potential years of life lost were 18 million for cancer compared to 15 million for heart disease (Ref. 46).

The risk of occurrence of cancer differs markedly for various sites. In 1990, lung cancer accounted for 35 percent of all cancer deaths in men. Colorectal cancer and prostate cancer each accounted for 11 percent of cancer deaths in men. The leading causes of cancer deaths among women were lung cancer (21 percent of cancer deaths), breast cancer (18 percent), and colorectal cancer (13 percent) (Ref. 46).

2. Dietary Fiber

Dietary fiber is comprised of components of plant materials that are resistent to human digestive enzymes (Refs. 12 and 24). These components are predominantly nonstarch polysaccharides and lignin and may include, in addition, associated substances (Ref. 12). To date, the best documented and most widely accepted nutritional role for dietary fibers is for normal bowel function and health (Ref. 24). It is estimated that current dietary fiber intakes of 10 to 15 grams (g) per day (6 to 7 g per 1000 kilocalories) in the United States are less than optimal for meeting needs for normal bowel function and health (Refs. 22 and 24). Significant increases in this level of intake have been recommended frequently (Ref. 24).

Based on currently available analytical methods, dietary fiber is measured both as total dietary fiber and as the subcomponents of soluble and

insoluble fibers (Ref. 24). Until recently, epidemiologic and other human studies were not able to evaluate total dietary fiber intake because the majority of food composition tables contained no values for total dietary fiber content of foods. In addition, no standardized definitions of dietary fiber or dietary fiber components have been agreed upon.

Naturally occurring fibers in food are usually a mixture of insoluble fibers such as cellulose and lignin, soluble fibers such as pectins, gums, and mucilages, and combinations of soluble and insoluble fibers such as hemicelluloses (Ref. 25). The proportions and types of fiber subcomponents vary among foods (e.g., oatmeal contains relatively large amounts of soluble fiber, while whole wheat bread contains relatively large amounts of insoluble fiber). Fiber content also varies within a food item or food group depending on maturity of the plant, storage and ripening conditions, and food processing techniques used, if any.

In evaluating the biological effects and health consequences of total dietary fiber, dietary fiber intake has been expressed as:

(a) As total dietary fiber or as the major fiber subcomponents (soluble and insoluble fibers);

(b) Fiber-containing foods (e.g., whole grains, legumes, fruits, vegetables);

(c) Fiber-rich food isolates (e.g., wheat bran, oat bran, corn bran, soy isolates); or

(d) Isolated and purified fibers (e.g., cellulose, pectins, lignin).

3. Basis for Evaluating a Relationship Between Dietary Fiber and Risk of Cancer

Interest in a possible role of dietary fiber in reducing the risk of cancer was stimulated by Burkitt and Trowell's suggestion that the rarity of cancer of the large intestine in Africa may be the result of a protective effect of dietary fiber (Ref. 5). These authors also suggested that fiber may be protective against other diseases that are common in the west, such as coronary heart disease and colorectal cancer. Subsequently, considerable research has been conducted on the role of dietary fiber and its relationship to risk of cancer at various sites.

Populations consuming diets rich in fiber-containing foods (vegetables, fruits, and grains) have significantly lower rates of cancer of the colon, breast, lung, oral cavity, larynx, esophagus, stomach, bladder, uterine cervix, and pancreas than populations consuming diets low in fiber-containing foods (Refs. 46 and 47). Available evidence also shows that populations consuming diets high in fiber also tend to consume diets that are low in fat and total energy (calories), high in vitamins and minerals (including vitamin A precursors and vitamin C), high in plant foods, and low in animal foods. Thus, it has not usually been possible to separate the effects of dietary fiber from those of other dietary components or a combination of dietary components.

Estimations of the impact of dietary fiber and other dietary components on total cancer incidence have been based on evidence regarding established relationships between dietary factors and cancer risk, the dramatic shifts in site-specific cancer rates among migrants to the United States, secular trends in cancer for which a dietary etiology is likely, and supportive evidence from animal experiments (Ref. 30).

The strongest support for a possible protective effect of fiber-rich diets is for cancers of the colon and rectum (colorectal cancers), the second leading cause of all cancer deaths in the United States (Ref. 46). Most of the epidemiologic associations between dietary fiber and risk of cancer relate to cancer of the colon. Virtually all laboratory animal studies on the topic of dietary fiber and cancer have focused on colon carcinogenesis.

The specific health claim topic described in the 1990 amendments was "dietary fiber and cancer." FDA, however, limited its review of the scientific evidence to cancers of the colon and rectum. This limitation was deemed appropriate because, as noted above, the great majority of epidemiologic and intervention studies have focused on colon cancer, as have virtually all animal studies in this area.

FDA recognizes that some fibers have been reported to modify the biological actions of hormones and thus reduce the risk of hormone-related cancers such as breast cancer (Ref. 22). Lanza et al. (Ref. 22) reviewed studies relating diets rich in fruits, vegetables, or grains and decreased risk of breast cancer, and also discussed mechanisms by which dietary fiber may modify risk of cancer at this site. FDA also recognizes that dietary fiber has also been studied with respect to its possible involvement in risk of stomach, ovarian, and endometrial cancers. Because the number of studies of the association between dietary fiber and cancers at these other sites is limited, review of such studies is not included in this document. The relationship of dietary fiber to cardiovascular disease is addressed in a companion document published elsewhere in this issue of the Federal Register. The relationships of antioxidant vitamins and cancer and f and cancer are addressed in two other companion documents also published elsewhere in this Federal Register.

C. Regulatory and Legislative History

1. Early Claims for Dietary Fiber

Claims for health benefits to be derived from consuming fiber-containin foods have been made for over 100 years. Early interest focused on the benefits of wheat bran as a promoter o regular bowel function. Claims for wheat bran on breakfast cereal packages were popular in the early 1900's, and the importance of adding "bulk" to the diet by the addition of dietary fiber was emphasized in advertisements promoting the benefits of certain fibers as aids to digestion an in relieving constipation. Such claims o packages were largely unregulated unti after the passage of the act in 1938. Under the act, such claims evidence an intent that the products are to be used as drugs, and therefore, subjected the products to the requirements of drug law. As a result, the use of health-related claims on cereal products virtually stopped until recently.

On November 22, 1941, the agency published regulations that included labeling requirements for "nondigestibl carbohydrates" (6 FR 5921). At that tim foods having a high fiber content were valued because decreases in caloric density were achieved when such products were added to foods such as bread. Based on the analytical procedures available at that time, the fibrous plant components of food had t be labeled as "crude fiber," which is compositionally and quantitatively different from dietary fiber.

During the late 1970's, FDA sought to revise its regulations to include as fiber other fractions of carbohydrates, in addition to crude fiber, that are not digested by human enzymes. In doing so, the agency noted that the scientific evidence linking fiber to health outcomes was limited. In the Federal Register of December 21, 1979 (44 FR 75990), the agency stated that "some advocates of higher fiber diets have theorized that the incidence of bowel cancer and other intestinal diseases may be related to the decreased amoun of fiber in western diets * * * and that the relationship of dietary fiber to healt remains controversial." Currently § 105.66 (21 CFR 105.66) provides for th declaration of nonnutritive substances, but there is no regulation for declaratio of fiber.

2. Food Additive Status

Substances that are added to food may be categorized based on their use as generally recognized as safe (GRAS) ingredients, food additives, or substances subject to a sanction or approval granted by the FDA or the United States Department of Agriculture prior to September 6, 1958. The use of substances may be GRAS under the general principles set forth in § 170.30 (21 CFR 170.30), listed as GRAS in part 182 (21 CFR part 182), or affirmed as GRAS in part 184 (21 CFR part 184). FDA's listings of food additives and affirmations that the use of a substance for direct addition to food is GRAS generally include the particular food categories in which (as defined in § 170.3(n)), and specific technical effects for which (as defined in § 170.3(o)), the substance may be used.

"Fiber" is not considered to be either a food category or a technical effect according to the above definitions, and ingredients that are added to food are therefore not regulated as "fiber." However, FDA has regulated a number of isolated or purified fibers for specific technical effects in various food categories. For example, xanthin gum is listed as a food additive for use as a stabilizer, emulsifier, thickener, suspending agent, bodying agent, or foam enhancer (§ 172.695 (21 CFR 172.695)); methylcellulose is listed as a multiple purpose GRAS substance (21 CFR 182.1480); and pectins are affirmed as GRAS for use as an emulsifier, stabilizer, or thickener (§ 184.1588). Guar gum is affirmed as GRAS for specific conditions of use that include those as an emulsifier, formulation aid, firming agent, and thickener (§ 184.1339). Guar gum has not been listed for use as a source of fiber, and under some circumstances, it has been shown to cause esophageal blockage and thus, to be a health hazard. These and many other isolated or purified gums and fibers have no established history of food use or safety as fiber supplements.

3. Dietary Fiber and Cancer as Subjects of Health Claims

Prompted by the use, beginning in 1984, of information on high-wheat bran cereal packages stating that high fiber diets may reduce the risk of cancer, and by issuance of interim dietary fiber recommendations by the National Cancer Institute, FDA proposed in 1987 to amend the food labeling regulations to allow the use of health messages (hereafter, the term "health claim" is used for consistency with section 403(r) of the act) on labels and food labeling (52 FR 28843, August 4, 1987). The agency stated that food labeling could have an important influence on the public s food choices, and that truthful, nonmisleading health claims could increase the consumer's understanding of health benefits that can result from adhering to a sound and nutritious diet. This proposal set forth criteria for the evaluation of health claims.

In the **Federal Register** of February 13, 1990 (55 FR 5176), FDA published a reproposed rule on health claims that withdrew the 1987 proposal and proposed to establish procedures for permitting valid and reliable consumer information on food labels. The agency noted that the 1987 proposal was too ambiguous to be workable in preventing misleading claims. FDA thus proposed to issue tighter requirements for health claims. The agency also proposed to evaluate the scientific evidence on six possible topics for claims, including dietary fiber and cancer.

On November 8, 1990, the President signed the 1990 amendments, that authorize FDA to issue regulations concerning claims on the label or labeling of foods that characterize the relationship between a substance and a disease or a health-related condition. As stated above, this law identified 10 substance-disease topics, including dietary fiber and cancer, that FDA is to consider to determine whether they are appropriate subjects of health claims.

D. Evidence Considered in Reaching the Decision

As noted above, the strongest support for a possible protective effect of fiber-rich diets is for colorectal cancers, major causes of cancer deaths in men and women in the United States. For this reason, FDA limited its review of the scientific evidence to the topic of dietary fiber and cancers of the colon and rectum (colorectal cancers). Most of the epidemiologic associations between dietary fiber and risk of cancer relates to cancer of the colon and virtually all laboratory animal studies in this topic area have focused on colon carcinogenesis.

The agency has reviewed the relevant scientific evidence on dietary fiber and colorectal cancers. The scientific evidence included descriptions of evidence reviewed and conclusions reached in Federal Government documents including "The Surgeon General's Report Nutrition and Health" (Ref. 47), the Department of Agriculture and the Department of Health and Human Services "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 45), and the Department of Health and Human Services' "Healthy People 2000, National Health Promotion and Disease Prevention Objectives" (Ref. 46). The agency also reviewed the evidence and conclusions in other reviews by recognized scientific bodies including the Life Sciences Research Office (LSRO) report on "Physiological Effects and Health Consequences of Dietary Fiber" (Ref. 24), the National Academy of Sciences (NAS) "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 30), the National Research Council's (NRC) "Recommended Dietary Allowances" (Ref. 31), and the World Health Organization's "Diet, Nutrition, and the Prevention of Chronic Diseases" (Ref. 51).

The agency updated these reports by independently reviewing all human studies and all review articles published since the Federal Government documents and other documents mentioned above had completed their reviews of the literature on the relationship of dietary fiber and colorectal cancer. FDA considered animal studies to the extent that they clarified human studies or suggested possible mechanisms of action.

FDA also contracted with LSRO to independently evaluate current evidence since the fiber report LSRO issued in 1987 (Ref. 25). Finally, to ensure that its review of relevant evidence was complete, FDA requested in the **Federal Register** of March 28, 1991 (56 FR 12932), scientific data and information on the 10 specific topic areas including dietary fiber and cancer identified in section 3(b)(1)(A) of the 1990 amendments. The agency reviewed and considered comments submitted in response to the **Federal Register** notice in developing this document.

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

Responses to the March 28, 1991 **Federal Register** notice were received from 3 professional organizations, 10 industry and trade associations, the Canadian Government, 1 consumer association, and an individual consumer.

One of the professional organizations urged caution in determining the use of health claims on foods, and another called attention to the need for FDA to use independent judgment with regard to the use of health claims on dietary supplements. A third professional organization pointed out that the protective effect of fiber against cancer cannot be ascribed to dietary fiber alone. The comment stated that the interaction of fiber with other nutrients

in the diet must also be considered. The comment also expressed concern that food label claims would be misunderstood by the public.

Among 10 comments received from dietary supplement or food manufacturers and related trade associations, 7 submitted comments and evidence, including some unpublished studies, that supported their position that health claims on fiber and cancer should be allowed on foods. One acknowledged that although the evidence is usually considered inconclusive, there is enough evidence to support the view that increased consumption of food sources of fiber is associated with reduced rates of cancer (colorectal and breast). All scientific data submitted are discussed in the scientific summary portion of this document.

The Director General, Food Directorate, Health and Welfare, Canada submitted information on the regulatory status of health claims in that country. The Canadian Government is not in favor of health claims on fiber-containing foods because it is difficult to disassociate the effect of fiber from the metabolic effects of fat and energy intake that also are claimed to influence the development of colorectal cancer. Although it has been estimated that cancer incidence can be reduced by 35 percent by dietary changes, "it has been remarkably difficult to identify specific components of the diet that increase risk or provide protection in individuals" (Ref. 28). The comment said that this finding does not diminish the importance of diet as a factor in the maintenance of health but reinforces the importance of the whole diet rather than the contribution of individual components.

II. Review of the Scientific Evidence

A. Federal Government Documents

"The Surgeon General's Report Nutrition and Health" (Ref. 47) reviewed human and animal studies of fiber and colorectal cancer and noted that among epidemiologic studies, international correlation studies are the most consistent source of support for the relationship. The report found that case-control studies provided less consistent support, but that many of the epidemiologic studies were limited by the lack of information about the type of fiber consumed. The report also noted that rodent studies suggest the importance of type of dietary fiber, but the relevance of these animal models to human cancer needs to be determined. The report concluded that "while inconclusive, some evidence also suggests that an overall increase in intake of foods high in fiber might decrease the risk for colon cancer." The role of various types of fiber that differ in their effects on water-holding capacity, viscosity, bacterial fermentation, and intestinal transit time has not been resolved (Ref. 47). The report concluded that current evidence suggests the prudence of increasing consumption of whole grain foods and cereal products, vegetables (including dried beans and peas), and fruits (Ref. 47).

USDA/DHHS' "Nutrition and Your Health, Dietary Guidelines for Americans" (Ref. 45) noted that populations such as those in the United States with diets low in dietary fiber and complex carbohydrates and high in fat, especially saturated fat, tend to have more heart disease, obesity, and some cancers. The guidelines stated that just how dietary fiber is involved is not yet clear, and that the benefit from a higher fiber diet may be from the food providing the fiber rather than from the fiber alone (Ref. 45). The dietary guidelines recommended that the American population choose diets with plenty of vegetables, fruits, and grain products rather than use of fiber supplements. Excessive use of fiber supplements is associated with greater risk of intestinal problems and lower absorption of some minerals.

In "Healthy People 2000," the Public Health Service and the Department of Health and Human Services identified increased consumption of complex carbohydrates and fiber-containing foods by adults as a specific risk reduction objective (Ref. 46). Recommendations included increasing consumption of vegetables (including legumes) and fruits to 5 or more servings daily, and increasing consumption of grain products to 6 or more daily servings. The report noted that dietary patterns with higher intakes of vegetables (including legumes), fruits, and grain products are associated with a variety of health benefits, including decreased risk for some types of cancer (Ref. 46).

There are several unresolved issues related to dietary fiber and cancer prevention (Ref. 46). For example, the role of specific types of fiber has not been delineated. Other natural substances present in plant foods, such as carotenoids, indoles, and flavonoids might also be contributing to the observed protective association for certain cancers (Ref. 46).

B. Other Reviews by Recognized Scientific Bodies

Several other reviews by recognized scientific bodies of the role of diet, nutrition and health have been published recently (Refs. 24, 25, 30, 31, 51, and 52). The conclusions regarding dietary fiber and cancer reached in these reports are similar to those reached in the Federal Government reports above.

An expert advisory committee was convened in 1985 by the Health Protection Branch of the Department of National Health and Welfare of the Canadian Government to advise them on scientific and regulatory issues related to dietary fiber (Ref. 52). While this report did not specifically review the area of fiber and cancer, it did review broad issues related to dietary fiber in foods. The committee noted that the relationship between the physico-chemical properties of dietary fibers and their physiological effects is difficult to evaluate due to the complexity of the interactions of mixed fibers in foods and to, in some cases, the lack of uniformity in testing procedures. The committee also recommended that manufacturers of food products, to which non-native and/or novel fibers have been added to increase dietary fiber content, may be required to provide evidence substantiating the safety and efficacy of these products in terms of accepted physiological effects. Non-native fibers were defined as fibers from traditional foods but not naturally occurring in the foods to which they have been added; novel fibers were defined as those which have not traditionally been part of the human diet. The committee also recommended that manufacturers of products which have been substantially enriched with native fibers should also be prepared to provide proof of efficacy and safety on request.

LSRO concluded in its 1987 report that dietary fiber is an integral part of a healthy diet (Ref. 24). However, it also concluded that the available evidence is not sufficient to support specific, quantitative recommendations on the role of dietary fiber for reducing the risk of specific diseases in the general, healthy population. The report noted that correlational studies using data from different countries have suggested a protective effect of dietary fiber against colon cancer, but that such studies cannot adequately determine whether high fiber intake per se or the low fat intake associated with consumption of fiber-rich foods is responsible for the observed associations (Ref. 24). The report noted

that most international correlational studies are based on the same Food and Agricultural Organization (FAO) data base and thus lacked independence. The LSRO report concluded that studies correlating fiber intake and cancer incidence within a single population generally observed weaker associations than the international studies. In reviewing the case-control studies of fiber intake and colon cancer, the report noted inconsistencies in the results. Nine studies showed fiber-containing foods to provide a protective effect, eight studies showed no effect, and three studies suggested that fiber may be a risk factor for colon carcinogenesis. LSRO concluded (Ref. 24) following a review of animal studies, that only particular types of fiber (especially fiber from wheat bran) are protective against chemically-induced colon cancer in animal models.

The LSRO report (Ref. 24) recommended consumption by the healthy adult population of a wide variety of foods, such as whole-grain products, fruits, and vegetables, leading to a dietary fiber intake range of 20 to 35 g per day (approximately 10 to 13 g per 1000 calories).

The 1989 NAS report "Diet and Health" (Ref. 30) also recommended increased consumption of vegetables, fruits, breads, cereals, and legumes. The report concluded that the evidence for a protective role of fiber in colon cancer was inconclusive. The report noted inconsistency in the results of epidemiological studies, and that animal studies suggested that the type of dietary fiber is important in modulating the effects of a colon carcinogen. The NAS report also noted that the effects attributed to fiber in some studies may actually be produced by some other components of the diet. Thus, even where the evidence is strongest, it has not been possible to adequately separate the effects of fiber from those of other components of the diet (e.g. total calories, fats, vitamins, minerals, and nonnutritive constituents of fruits and vegetables) and nondietary factors (e.g. socioeconomic status) (Ref. 30). The overall assessment of the evidence by the NAS report was as follows: "In general, the evidence for a protective role of dietary fiber per se in coronary heart disease, colon and rectal cancers, stomach cancers * * * is inconclusive." (Ref. 30).

The NRC's "Recommended Dietary Allowances" (Ref. 31) stated that the consumption of diets rich in plant foods, and therefore fiber, is inversely related to the incidence of cardiovascular disease, colon cancer, and diabetes and noted that because an increase in dietary fiber consumption is almost invariably associated with a change in other dietary constituents, it is difficult to establish a clear relationship with dietary fiber alone (Ref. 31). The NRC recommends that a desirable fiber intake be achieved not by adding fiber concentrates to the diet, but by consumption of fruits, vegetables, legumes, and wholegrain cereals, which also provide minerals and vitamins (Ref. 31).

The reports summarized above were in agreement in their recommendations that Americans should increase their intake of fiber-rich foods. The reports are also in agreement in their conclusions that it is not clear if the relationship between fiber-rich foods and lower rates of cancer and other chronic diseases is the result of the fiber content of the foods or of other nutrients contained in these foods. Thus, virtually all recent dietary guidelines encourage the increased consumption of fiber-rich foods rather than fiber.

In its report "Diet, Nutrition, and the Prevention of Chronic Diseases," (Ref. 51), the World Health Organization stated that dietary factors are known to influence the development of a wide range of chronic diseases, including cancer, but the relationships between specific dietary components and cancer are much less well-established than those between diet and cardiovascular disease. The report noted that for populations in developed countries, some epidemiologists estimate that 30 to 40 percent of cancers in men and up to 60 percent of cancers in women are attributable to diet (Ref. 51). Although several studies demonstrated positive associations between the risk of colorectal cancer (primarily colon cancer) and dietary fat, the data relating dietary fiber to colorectal cancer are equivocal. The WHO report concluded that it is not clear whether dietary fiber is protective or whether the apparent effect is due to other food constituents (Ref. 51).

The 1990 Canadian Government document *Nutrition Recommendations—Report of the Scientific Review Committee* (Ref. 28) reviewed the literature on nutrient requirements and on various relationships between diet and disease. The goal of the document was to provide guidance in the selection of a dietary pattern providing essential nutrients, while reducing the risk of chronic disease (Ref. 28). With respect to cancer studies, the document noted that international epidemiologic studies show an inverse relationship between colon cancer mortality and fiber content of diets. The difficulty with epidemiologic studies, the document pointed out, is that they suffer from an inability to "disentangle the effect of the fiber content in the diet from the effect of fat and energy intake" which can influence the development of colorectal cancer (Ref. 28). The document concluded that various studies have provided inconsistent results and some have cast doubt on the beneficial effect of fiber. The Canadian recommendations are to increase present intakes of dietary fiber from a variety of carbohydrates and fiber-rich foods. The addition of large amounts of a single source of purified fiber to the diet was not recommended (Ref. 28).

In 1991, LSRO reviewed scientific studies that have become available since publication of its earlier report (Ref. 24). LSRO (Ref. 25) found no new evidence to support an association between increased intake of dietary fiber and decreased risk of cancer. The report concluded that it remains to be determined whether the observed effects of fiber are due strictly to fiber, to other components of fiber-rich food, to displacement of fat or calories from the diet by fiber, or to a combination of these (Ref. 25).

C. Review of the Scientific Evidence

1. Selection and Evaluation of Studies

a. *Selection of studies.* The criteria used to select pertinent studies required them to be publicly available in English, to provide a description of the study design and results that is adequate to permit an evaluation of the study, to include direct measurements or quantitative estimates of total dietary fiber intake as a single substance or as a component of foods, and to include direct measurement of risk of colorectal cancer (prognostic indicators, incidence, development, prevalence, or mortality).

Several types of human studies provide information on the role of dietary fiber in colorectal cancer. Correlational studies use grouped data to examine the relationship between dietary exposure and health outcome among populations. These studies do not examine relationships among individuals and have traditionally been regarded as useful for generating, rather than testing, hypotheses regarding diet-disease relationships. Analytic epidemiologic studies involve comparisons of individuals and have been regarded as providing the strongest type of observational evidence in human populations. In case-control studies, the relationship of an attribute (in this case,

a dietary component) to a disease is examined by comparing persons who already are diagnosed with cancer (cases) to persons without cancer (controls). A limitation of the case-control study is that diet is assessed in the cases after diagnosis, so that cases may unintentionally overestimate or underestimate dietary intakes of specific foods. Prospective cohort studies compare individuals who have been exposed to a risk factor to those who have not and observe individuals over time to determine if disease develops. In cohort studies, diet is assessed at the beginning of the study before cancer develops.

b. *Evaluation criteria.* FDA evaluated the results of studies in humans and animals against general criteria for good experimental design, execution, and analysis. The strengths and weaknesses of different kinds of epidemiologic studies and the methodologies for dietary assessment relevant to risk of chronic diseases, as well as suggestions on weighing of available evidence, are reviewed and discussed in the proposal on general requirements for health claims (published elsewhere in this issue of the **Federal Register**) and are also reviewed elsewhere (Ref. 30).

The criteria that FDA used in evaluating epidemiology studies included reliability and accuracy of the methods used in food intake analysis and measurement of disease endpoints, choice of control subjects, representativeness of subjects, control of confounding factors (for example, intake of fat and other nutrients; intake of vegetables), potential for misclassification of individuals with regard to dietary intakes, and presence of recall bias and interviewer bias.

The criteria that FDA used in evaluating studies in animals included whether components (for example, fiber) added to experimental diets were within physiological ranges of intake, whether there was control of confounding factors (for example, through use of isocaloric diets), whether the animal species was appropriate as a model for human carcinogenesis in response to dietary modification, and whether the numbers of animals used, the duration of exposures, the periods of observation, and methods used for assessment of disease endpoints, were appropriate.

FDA assessed the weaknesses and strengths of individual studies. FDA then assessed the strength of the overall evidence derived from the Federal Government reports, the other reports cited above, and the update of the scientific literature, using factors including the strength of associations, consistency of findings, specificity of reported associations, evidence for a dose-response relationship, and biological plausibility. FDA's conclusions reflect the strength, consistency, and the degree of concordance among results obtained from a variety of types of studies.

FDA also considered several factors identified by the NAS in its evaluation of the scientific basis for a relationship between intake of dietary fiber and cancer (Ref. 30). The NAS report cautioned that analysis of study results based on measures of total dietary fiber alone could be misleading because of the complex nature of the dietary substances subsumed under the term "fiber." In many studies, no quantitative data were given on the intake of total dietary fiber or of subcomponents of fiber. NAS (1989) also stated that in view of the importance of fat intake and total caloric intake, data from studies that are controlled for energy, fat, and other nutrients are the most useful. Fiber intake is correlated with caloric intake, which in turn is correlated with fat intake. Finally, the report cautioned that homogeneity of dietary fiber intake within a population may make it difficult to detect an effect of high fiber diet on incidence of cancer (Ref. 30).

2. Human Studies

The Federal Government reports and the other reports cited above noted that the effect of fiber-rich foods was best documented relative to risk of colorectal cancer. FDA reviewed all publicly available colon and rectal cancer studies in human subjects published from 1988 to the present. This review was undertaken to determine if more recent data provided additional evidence on an association between dietary fiber and risk of colorectal cancers, and if new results would alter the conclusions of the earlier reports.

a. *Correlational studies.* A brief summary of correlational studies relating to associations between dietary fiber and risk of colorectal cancer reviewed in "The Surgeon General's Report" (Ref. 47) and in reports by other scientific bodies is presented here. Many correlational studies have suggested a protective effect of dietary fiber against colon cancer (Refs. 24 and 47). Twenty-one of 24 correlational studies reviewed in "The Surgeon General's Report" (Ref. 47) identified an inverse association between intake of dietary fiber, cereals, or vegetables and occurrence of colon cancer. Three of the 24 studies showed no effect. One international study (Ref. 26) found an inverse association between colon cancer and total dietary fiber and reported a protective effect of cereal fiber, even after adjustment for intake of fat or meat. Some of these studies also showed correlations between intake of other nutrients and colon cancer. Thus, while patterns of eating foods high in fiber showed good correlation with low colon cancer rates, other dietary components might also be influencing this association (Ref. 47).

Two recent studies (Table 1) have correlated colorectal cancer mortality with population-based dietary intake data. Rosen et al. (Ref. 37) correlated colon cancer mortality rates from 1969 to 1978 with estimates of dietary intake of fiber for 24 counties in Sweden. Dietary fiber intake was calculated from household food expenditure data (excluding foods eaten outside the home) for 1978. Results showed a strong negative correlation (inverse relationship) between dietary fiber and colorectal cancer in both men ($r = -0.75$) and women ($r = -0.67$) ("r" means simple correlation coefficient), and this association was not altered by controlling for fat intake. Rosen et al. (Ref. 37) observed similar correlations for high-fiber breads. No effects of vegetable consumption on colorectal cancer were observed (Ref. 37).

Daily per capita total dietary fiber intake was estimated to be 12 g based on expenditure data. Regional data showed a high intake of milk and fat as well as fiber in areas with low mortality rates from colorectal cancer. A major limitation of correlational studies is that dietaty intakes are not necessarily assessed in the individuals who develop the disease under investigation. This limitation and regional differences in dietary intakes may explain why high intakes of fat, fiber, and milk were associated with low mortality rates from colorectal cancer in the study by Rosen (Ref 37).

Morales Suarez-Varela et al. (Ref. 29) (Table 1) undertook a correlational study of diet and rectosigmoid cancer in Spain. The investigators correlated standardized mortality and morbidity data from rectal and sigmoid colon cancer in 50 Spanish provinces with dietary fiber (type unspecified) consumption estimated from food composition tables of the National Statistical Institute. Consumption of vegetable fats, butter and pork lard, total animal fats, and fiber showed no correlation with provincial morbidity and mortality due to rectal cancer. Sex-specific standardized morbidity ratios for men showed a modest positive correlation (0.3344; $p < 0.01$) of fiber consumption with rectosigmoid colon cancer morbidity. These observations are difficult to interpret because the

study combined data from rectal and lower (sigmoid) colon cancer cases.

b. *Case-control studies.* In several recent case-control studies, patients with colon cancer and matched controls were interviewed about previous fiber intake (Table 2). Kune et al. (Ref. 21) (Table 2), in a study of 715 colorectal cancer cases and controls, analyzed data on total fiber, vegetable fiber, and fruit fiber intake. Dietary information covering the previous 20 years was obtained from subjects by interview. Although uncontrolled analysis for total fiber, vegetable, fruit, and cereal fiber gave a negative association with colorectal cancer, the effect was removed when micronutrients, fats, and energy were controlled. By examining interaction effects, the combination of high fiber intake and high vegetable intake was found to be protective, although neither was independently protective. The source of the fiber (cereal, vegetable, or fruit) did not alter the interaction. The types of fiber involved (soluble or insoluble) were not identified (Ref. 21).

Tuyns et al. (Ref. 44) (Table 2) conducted a case-control study of 453 colon cancer patients, 356 rectal cancer patients, and 2,851 population-based controls in 2 Belgian provinces. Cases were asked about their usual food intakes over 1 week before the onset of illness and controls at the time of interview. Only 50 percent of the case series were successfully interviewed. Logistic regression analysis was used to estimate the relative risk of colon and rectal cancer, controlling for age, sex, province, total calories, and other nutrients. Dietary fiber intake was significantly negatively associated with both colon and rectal cancer (i.e., the higher the fiber intake, the lower the incidence of these cancers), and there was a negative linear trend indicative of an intake response (Ref. 44). This trend was not affected by adjustments for calorie intake. However, the low response rate of the cases (50 percent) may have introduced selection bias and substantially reduces the confidence that can be placed in the results.

West et al. (Ref. 48) (Table 2) studied dietary intake in 231 colon cancer cases from the Utah Cancer Registry and 391 controls identified by random digit dialing. A stratified random sample of control individuals within the selected households was chosen to reflect sex, age within 5 years, and county of residence of cases. Food intake was assessed by a food frequency questionnaire for the 2 to 3 years prior to the interview. Interviews were completed for 71 percent of cases and 74 percent of controls. Odds ratios and multiple logistic regression analysis were used to estimate the risk of colon cancer controlling for age, body mass index, and energy intake, but not for other dietary factors. Increased crude fiber intake was associated with a decreased risk of colon cancer for both males and females. Ninety percent confidence intervals were used in the statistical analysis and this finding was significant at the 0.10 level.

A detailed analysis of dietary fiber components was undertaken in a case-control study in western New York of 428 colon cancer cases, 422 rectal cancer cases, and neighborhood controls (Refs. 9 and 10) (Table 2). Cases were identified from hospital pathology reports. Sixty-five percent of colon cancer patients, 54 percent of rectal cancer patients, and 53 percent of eligible controls were interviewed regarding frequency of consumption of foods for 1 year prior to onset of symptoms. Total dietary fiber was classified by source from grain, or fruit, or vegetables, and for each of these, the soluble and insoluble components were identified. Insoluble fiber from each source (grain, fruit, or vegetables) was further classified as hemicellulose, cellulose, or lignin. Conditional logistic regression analysis, with adjustment for fat intake, was used to estimate the impact of total fiber and each of five fiber components from grains and fruit or vegetables on risk of colon and rectal cancer. Separate analyses were performed for males and females. Reduction in risk of colon cancer was associated with intake of grain fiber in both males and females and with fiber from fruit or vegetable sources for males only. Insoluble grain fiber was more strongly associated with reduction in risk of colon cancer than soluble fiber. Analysis of risk of rectal cancer showed a protective effect of fruit or vegetable fibers but not grain fibers. There were no differences in the effects of soluble and insoluble fiber. However, the analysis did not control for other components of fruits and vegetables that might affect cancer risk. Furthermore, the low response rates for cases and controls may introduce selection bias.

Wohlleb et al. (Ref. 50) (Table 2) conducted a small case-control study of colorectal cancer (43 patients and 41 controls) in men at a U.S. Veterans Administration hospital. Demographic traits, medical history, occupational history, use of alcohol and tobacco, and other information were obtained by questionnaire that also collected data about weekly intakes of 55 food items (that is, current diet was surveyed). Consumption of cauliflower (a cruciferous vegetable) was significantly associated with fewer cancers in this study. Consumption of rolled oats appeared as a significant protective factor against colorectal cancer, and other high-fiber foods (wheat bran and unpeeled apples) were apparently protective (Ref. 50).

A case control study conducted in Stockholm, Sweden, involved 452 subjects with colon cancer, 268 subjects with rectal cancer, and a population based control group (Ref. 8) (Table 2). Dietary data for the previous 5 years was obtained by a food frequency questionnaire. Interviews were completed for 76 percent of cases and 87 percent of controls. A protective effect of high fiber intake against colon cancer was found in men (RR = 0.5) but not in women (RR = 1.2). Fiber appeared to be protective against rectal cancer in both sexes (RR for all subjects = 0.5). The data were analyzed controlling for year of birth and protein intake but not for other nutrients. There was an interaction effect observed between protein and fiber intake such that fiber had a greater protective effect in those consuming a low protein diet.

A case-control study performed in Utah (Ref. 40) (Table 2) involved 231 colon cancer cases and 391 controls. Subjects were interviewed about diet for the 2 years prior to diagnosis. Consumption of fruits, vegetables, and grain was estimated by a food frequency questionnarie. Fiber intake was calculated from several food tables, and in some cases actual analysis of foods was performed to allow assessment of the effects of chemically-defined fiber fractions. Body mass index, caloric intake, membership in the Mormon church, and age were controlled for by statistical adjustment. The effect of fiber varied with the chemical type and food source. Intake of fruits and vegetables was negatively related to risk of colon cancer in males and females. Intake of grain fiber was not protective. The effects of neutral detergent fiber or dietary fiber as determined by the method of Bitner were weak and inconsistent. Fiber effects, when detected, were usually of greater magnitude in males. This study is one of the few to examine the effects of several analytically defined fiber fractions. The results suggest that fibers from different food sources have different effects.

Lee et al. (Ref. 23) (Table 2) conducted a case-control study of 132 colon cancer cases and 71 rectal cancer hospital cases in Singapore. Dietary information was obtained about usual diets consumed 1 year prior to the interview.

Intakes of cruciferous vegetables and a high intake of vegetables relative to meats were generally protective against colorectal cancer. Fiber was protective for rectal cancer (OR = 0.46; $p < 0.05$) but not for colon cancer. Protective effects were reported for cruciferous vegetables (OR = 0.50 < 0.01). The authors urged caution in interpreting their data for rectal cancer, however, because of the small number of cases.

One study examined the dietary patterns of patients with colonic polyps (considered a precursor lesion to colon cancer) and of individuals without polyps. Hoff et al. (Ref. 15) (Table 2) assessed dietary intake from 5-day food records in a case-control study utilizing patients participating in endoscopic screening for colonic polyps. Nutrient intake of patients with and without polyps was compared. Patients were not aware of their polyp status when they completed the food intake records. Results revealed that patients with large polyps consumed significantly less total dietary fiber and less total carbohydrate than patients without polyps. Intake of vitamin C and cruciferous vegetables did not differ significantly among patients with or without polyps, although patients with multiple polyps had a significantly lower intake of cruciferous vegetables and vitamin C compared to patients with only a single polyp. Assessment of diets 1 to 2 years or more prior to onset of symptoms would have provided more useful information.

Benito et al. (Ref. 4) (Table 2) conducted a case-control study of 286 colorectal cancer patients, 295 age and sex-matched community controls, and 203 hospital controls on the Spanish island of Majorca. The participants were given a food frequency questionnaire covering the 6 months prior to the interview. Consumption of high-fiber vegetables was found to have no effect on the risk of colorectal cancer. No data on total fiber or its components were provided. Slattery et al. (Ref. 41) conducted a case-control study correlating diet prior to diagnosis with survival time in colon cancer patients. Dietary information for the 2 to 5 years prior to diagnosis of colon cancer was collected by interview. The highest quartile of fiber intake was associated with decreased survival time.

c. *Prospective studies.* In two recent prospective studies, dietary intakes of individuals were estimated at baseline by mailed questionnaire and then individuals were followed over time for occurrence of disease. Willet et al. (Ref. 49) (Table 3) in a study involving 6 years of followup of 88,751 female nurses (ages 34 to 59 years) found no evidence of a protective effect of intake of total crude fiber on colon cancer. A high intake of crude fiber from fruit, but not from vegetables or cereal, showed a significant protective effect but this effect was not statistically independent of intake of red meat.

Heilbrun et al. (Ref. 13) (Table 3) conducted a nested case-control study of 8,006 Japanese-American men in Hawaii, with 361 controls, 102 cases of colon cancer, and 60 cases of rectal cancers. Dietary intakes of crude fiber were based on a single 24-hour recall collected between 1965 to 1968. Cancer cases consumed an estimated 11.4 to 12.1 g per day of crude fiber while controls consumed 11.6 g of crude fiber per day. Proportional hazards models adjusted for age, and for alcohol intake in the cases of rectal cancer, were used to estimate the relative risk of colon and rectal cancer. The models included all micronutrients, fat, calories, saturated fat, protein, cholesterol, and carbohydrates. Fiber was protective in the low fat group when the cohort was divided into two groups at the median level of fat intake of colon cancer cases. When fat intake was less than 61 g per day, risk of colon cancer decreased as consumption of fiber increased ($p < 0.042$).

d. *Meta-analysis of epidemiologic studies.* Trock et al. (Ref. 43) performed a thorough review with reanalysis of data from all English-language epidemiologic studies concerning colorectal cancer and fiber, vegetables, grains, or fruit published from 1970 through 1988. The review included 23 case-control studies, 7 international correlation studies, 8 within-country correlation studies, 2 cohort studies, and 3 time-trend studies. Trock et al. (1990) made an aggregate assessment of the strength of evidence from numerous observational epidemiologic studies and meta-analysis of data from 16 of 23 case-control studies. Both types of analyses indicated that the majority of studies give support for a protective effect of fiber-rich foods against colorectal cancer. Risk estimates based on vegetable consumption were only slightly more convincing than those based on estimates of fiber intake. The authors noted that the data do not permit discrimination of the fiber and nonfiber effects of vegetables (Ref. 43).

e. *Intervention studies.* DeCosse et al. (Ref. 7) conducted a long term, randomized intervention study aimed at reducing rectal polyp recurrence in patients with familial polyposis. Adults patients (n = 58) having undergone previous total colectomy for familial polyposis were given daily supplements of vitamins C and E alone or with wheat bran, and rectal polyp number and size was assessed repeatedly over a 4-year period. Fiber appeared to reduce mean polyp size over time, especially if total intake of fiber was calculated as dietary sources plus fiber supplement. Thus, the authors concluded that benign large bowel neoplasia was inhibited by intakes of grain fiber supplements greater than 11 g per day. It is not known whether the results of this study can be applied directly to the much more common clinical situation of sporadic colonic polyps.

f. *Mechanistic studies.* The mechanisms by which fiber may affect colonic carcinogenesis are unknown. Proposed mechanisms include effects of fiber to:

(a) Dilute fecal bile acids which may have growth promoting effects on small adenomas;

(b) Reduce fecal mutagenicity;

(c) Alter fecal bulk;

(d) Increase fecal transit time;

(e) Alter colonic mucin;

(f) Change fecal pH; and

(g) Alter colonic cell proliferation.

Newer hypotheses have focused on the role of microbial fermentation in cancer prevention (Ref. 22). A number of studies have been performed in attempts to test which of these potential mechanisms may affect tumorigenesis.

FDA reviewed a number of studies that examined hypothesized risk factors for colon cancer such as cell turnover, fecal bile acids, and fecal mutagens. Such studies are helpful in determining possible mechanisms of action for effects of fiber or fiber-rich foods on carcinogenesis. Fiber type and amount can be carefully controlled in animal and human mechanistic studies. As a result, it should be possible to distinguish effects of fiber from effects of other components of fiber-rich foods.

Reddy et al. (Ref. 35), in a study involving supplementing the diet with a mixture of high-fiber oat and whole wheat bread, found a significant decrease in fecal secondary bile acid concentration and decreased fecal mutagenicity with increased fiber intake in the form of high-fiber bread.

Reddy et al. (Ref. 34), in a dietary intervention study, instructed subjects to eat a high fiber, low fat, low meat diet, similar to the "Pritikin"-type diet. The dietary intervention increased stool weight and decreased bile fecal acid concentration (effects that are thought to be protective against colon carcinogenesis). The interpretation of the study was complicated by significant weight loss in the subjects

and major dietary changes other than alterations in dietary fiber. The study design did not use a contemporaneous control group and did not attempt to crossover treatments.

In a well-designed study, Reddy et al. (Ref. 33) fed wheat bran, cellulose, or oat bran to human subjects in a randomized crossover design. Both wheat bran and cellulose reduced fecal mutagenicity, fecal bile acid concentration, and fecal neutral sterol concentration. These are all considered positive changes toward reducing colon cancer risk. Oat bran, however, did not significantly alter these parameters compared to those measured with the baseline "normal" diet.

Allinger et al. (Ref. 3) instructed subjects to increase their intake of fruits, vegetables, and grains, eliminate meat and eggs, and consume only fermented, rather than fresh, dairy products. The change in diet was conducted in three "shifts" (March, May, and August) to attempt to control for seasonal variability. The total dietary change resulted in increased fecal weight and decreased soluble fecal deoxycholic acid (both thought to be favorable changes for reduced risk of colon cancer). Because of the combined dietary approach, it cannot be determined whether the additional fiber or the other changes in the diet were responsible for the observed alterations in the fecal parameters.

Johansson et al. (Ref. 18), in another study utilizing the same subjects and diets, as Allinger et al. (1990), examined changes in fecal bacterial enzyme activities in response to the dietary modifications. The dietary change decreased the activity of three fecal bacterial enzymes considered to be important in colonic carcinogenesis. Most of the effect was apparently the result of dilution by increased stool volume. Moreover, the importance of these bacterial enzymes in the development of human colon cancer is unknown. It cannot be determined whether the additional fiber or the other changes in the diet were responsible for the observed alterations in the fecal parameters.

Alberts et al. (Ref. 2) examined rectal cell proliferation in a trial of wheat bran supplementation (13.5 g per day) in patients in whom colons were removed for treatment of colon cancer. Seventeen patients (aged 54 to 70 years), at high risk of recurrent colorectal cancer, participated in the 8-week study. Rectal cell proliferation was assessed by two methods both pre- and post-diet intervention. One method of assay showed a significant mean decrease in rectal cell proliferation after 2 months of wheat bran supplementation while the other showed no change.

Kashtan et al. (Ref. 19) found that 100 g of oat bran decreased fecal pH significantly in normal volunteers, while lesser quantities of oat bran did not produce significant reductions in fecal pH. Psyllium and wheat bran did not affect fecal pH. The importance of fecal pH in colon cancer has not been determined.

In a study by Friedman et al. (Ref. 11), human colonic cells were incubated in vitro with psyllium or bile salts. Small decreases in the cytotoxicity of the bile salts were noted with the addition of psyllium, and other alterations in cell growth were seen when various short chain fatty acids (products of bacterial digestion of fiber in the large intestine) were added. However, adding ungraded psyllium to a cell culture is not reflective of the bacterial metabolism of this material which occurs in the colon in vivo. No rationale is provided to relate the concentrations or relative proportions of short chain fatty acids added to the culture to the products of actual bacterial digestion of psyllium in vivo. Thus, the in vitro conditions in this study may not be physiological.

3. Animal Studies

As mentioned previously, most laboratory animal studies of dietary fiber and cancer have focused on colon cancer. Results of numerous animal studies are reviewed by LSRO (Ref. 24), in The Surgeon General's Report. (Ref. 47), and in "Diet and Health" (Ref. 30). Recent reviews include those (Refs. 17 and 32).

Effects of dietary fiber on colon carcinogenesis in animals are frequently studied following exposure of the animals to a compound such as 1,2-dimethylhydrazine (DMH) which is known to be carcinogenic to the colon. The animals are then fed varying amounts and types of dietary fibers and subsequent effects tumorigenesis are observed. The carcinogen is usually given weekly via a tube into the stomach or injection for a 5- to 10-week period. Tumors begin to develop within 2 to 3 months following completion of carcinogen treatment.

The 1987 LSRO (Ref. 24) report notes that studies using animal models to examine the role of various types of dietary fiber in the development of carcinomas of the colon provide conflicting results. One of the factors that has a major effect on the results of carcinogenesis studies is the type of dietary fiber fed to the animals. Many studies have shown that not all fiber types reduce experimental colon cancer. Dietary soybean bran and rice bran showed no effect on DMH-induced colon carcinogenesis in rats, while oat bran had an enhancing effect. Corn bran had either an enhancing effect or no effect on colon carcinogenesis, while 10 percent guar gum was shown to enhance tumor development. Most studies with wheat bran show an inhibitory effect. The 1987 LSRO (Ref. 24) report states that both the physical and chemical properties of a fiber source are probably important in determining its effects. Of all fiber types studied, the authors considered wheat bran to have the most consistent inhibitory effects on colonic tumor development.

Many factors besides the type of fiber fed were noted to affect the outcome of these studies, including the type and dose of carcinogen given, the sex and strain of animal, the total duration of the study, and whether the fiber was fed during the initiation phase (while carcinogen is being given) or during promotion (after completion of carcinogen treatment).

"The Surgeon General's Report" (Ref. 47) noted that wheat bran was found to be protective in most but not all animal studies. Results of animal studies of fibers such as corn bran, rice bran, oat bran, pectin, and guar gum were much less consistent. Some studies showed a protective effect, more tended to show a tumor-enhancing effect, and others showed no effect. "The Surgeon General's Report" (Ref. 47) concluded that the relevance of these animal models to human cancer needs to be determined.

The NAS, in "Diet and Health" (Ref. 30) cited a diversity of results (protection, enhancement, no effect) for nonhuman carcinogenesis studies of various types and amounts of fiber. The report concluded that the type of fiber is very important in determining its effects on colon carcinogenesis. NAS (Ref. 30) also noted that wheat bran has the most consistent inhibitory effect.

Animal studies published since 1987 in which animals were fed defined diets containing cellulose, wheat bran, or psyllium are reviewed briefly below.

Roberts-Anderson et al. (Ref. 36) fed 10 percent cellulose, 10 percent psyllium, or a fiber free diet to rats both during and after administration of a chemical carcinogen. Both fiber treatments reduced tumor incidence. Rats in the psyllium group gained considerably less weight than control rats, and the duration of the study was significantly shorter than most published tumorigenesis studies. The number of rats exposed to the carcinogen was also smaller than usual for studies of this type.

Heitman et al. (Ref. 14) fed rats 0, 5, or 15 percent cellulose during the phases of initiation or promotion or both. Cellulose at 5 or 15 percent showed statistically significant protective effects if fed during both initiation and promotion. Other combinations of cellulose feeding (promotion only, etc.) produced reductions that were not statistically significant. The authors correlated the antitumor effects of cellulose with its ability to inhibit DMH-induced cell replication during initiation. This study suggests a protective effect for cellulose when fed during both initiation and promotion.

Three recent studies evaluated the effect of wheat bran on colon carcinogenesis. Calvert et al. (Ref. 6) fed 10 percent wheat bran or wheat bran with bile salts added (sufficient to eliminate its effects on bile salt dilution) to rats during the promotion phase, after they had been exposed to the chemical carcinogen DMH. Wheat bran consistently reduced tumor incidence and multiplicity in this study. Added bile salts did not diminish this effect, suggesting that bile salt dilution is not the mechanism of the observed antitumor effect. Tatsuta et al. (Ref. 42) noted no effect of wheat bran on tumor development in their study. Wheat bran was fed during both initiation and promotion. Sinkeldam et al. (Ref. 39) fed 9 or 17 percent wheat bran to rats on low, medium, or high fat diets. Diets were consumed during both initiation and promotion. The 17 percent wheat bran diets eliminated the tumor enhancing effect of increasing levels of fat. If fat levels were moderate or low, 9 percent wheat bran enhanced tumorigenesis, while 17 percent wheat bran was inhibitory.

Thus, three recent studies with wheat bran report inconsistent effects on colon carcinogenesis. Differences in the timing of the feeding of wheat bran (promotion phase only versus initiation and promotion phases) or fat levels may partly explain these inconsistencies.

4. Other Relevant Information

Concerns have been raised about potential risks of ingesting isolated or purified forms of fiber (Ref. 24, 25, and 52). Side effects and possible adverse health effects of high intakes of dietary fiber have also been hypothesized by NAS (NAS, 1989). Excessive consumption of fiber supplements may result in more intestinal problems or poor absorption of trace minerals than would be expected from a high-fiber diet (Ref. 25). Safety concerns about more novel sources of fiber (e.g., gums and isolated sources of fibers) when consumed in large amounts or when consumed in nonfood forms have also been raised (Ref. 52). However, high dietary intakes of foods with naturally occurring fiber have generally not been found to have adverse health effects (Ref. 24 and 30).

5. Conclusions

Federal Government documents (Ref. 47) and the other referenced reports from recognized scientific bodies (Refs. 24, 25, and 30) concur that the evidence for a protective effect of dietary fiber in colon carcinogenesis is inconclusive. However, they do note the association of dietary patterns high in plant foods to reduce risk of cancer and other chronic diseases.

Of two recently reported correlational studies, one compared colorectal cancer mortality in Sweden with population-based dietary fiber intake data and found a strong negative correlation between intake of dietary fiber and colorectal cancer mortality in men and women, Rosen et al. (Ref. 37). In a second study, Morales Suarez-Varela et al. (Ref. 29) found no correlation between fiber intake and rectosigmoid cancer morbidity or mortality among 50 Spanish province Spain.

Dietary fiber is extremely heterogenous in nature (Refs. 12 and 21) and fiber-rich foods differ significantly in the amounts and types of fiber components they contain. The limited amount of analytical data on dietary fiber and various components of dietary fiber have impeded research on its health effects (Ref. 22).

Human studies on effects of dietary fiber intake and risk of cancer of the colon and rectum have differed in classification of dietary fiber (i.e., source, type, components) and in measurement of dietary intake (e.g., 24-hour recall, food frequency). The results of these studies have also differed. Of two recent case-control studies that were adequately controlled for other known components of fruits and vegetables, one study, Kune et al. (Ref. 21) reported no effect of dietary fiber per se but found an interaction such that those consuming diets high in fiber and vegetables experienced a reduced risk of colorectal cancer. Tuyns et al. (Ref. 44) reported a protective effect of dietary fiber and an intake response relationship.

Three other recent case-control studies did not control for micronutrients in vegetables and fruits. The results of these studies were inconsistent. West et al. (Ref. 48) reported an association of crude fiber with reduced risk of colon cancer. Freudenheim et al. (Refs. 9 and 10) observed no association of total fiber with colon cancer, but grain fiber was protective in men and women, and fruit and vegetable fibers were protective in men only. The same study showed fruit or vegetable fiber to be protective for rectal cancer (statistically significant only in men) regardless of soluble or insoluble components. In contrast to the results reported for colon cancer, grain fiber consumption was not associated with risk reduction in rectal cancer. De Verdier et al. (Ref. 8) reported that fiber was protective in men only, but an interaction was observed such that a low protein and high fiber diet led to a reduction in risk of colon and rectal cancer. Because none of these studies controlled for nutrients or other components in fruits and vegetables, it is not possible to determine if observed effects were due to fiber or to nonfiber components of fruits and vegetables.

Among two recently completed prospective studies, Willet et al. (Ref. 49) reported no effect of crude fiber or components when consumption of red meat was controlled. Heilbrun et al. (Ref. 13) reported no effect of dietary fiber on colon or rectal cancer. However, fiber was protective in those subjects with a fat intake below the median for the group as a whole.

A number of studies have examined effects of dietary fiber on possible risk factors for colorectal cancers. Such studies have examined effects of specific types of fibers on hypothesized risk factors for colorectal cancer. Generally favorable effects of some types of fibers on such factors have been reported. The actual risk factors for colorectal cancer are still incompletely understood, however. Thus, the significance of favorable effects produced by fiber feeding on particular parameters such as secondary bile acid concentration, fecal mutagenicity, fecal weight, fecal deoxycholic acid, and activity of fecal bacterial enzymes is not clear at this time. Additional studies are needed to establish which, if any, of these factors affect the development of human colon cancer.

Thus, evidence that has become available since the publication of the Federal Government and the other major reviews by recognized scientific bodies does not provide a basis for altering the conclusions of these documents which note a reduced risk for colon cancer with diets high in fiber-containing foods but not for fiber in isolation.

Results of studies of colon carcinogenesis in animals must be interpreted cautiously. Colon cancer is induced in animals by relatively

infrequent exposures to large doses of a known, potent carcinogen, while in human colon cancer, carcinogen exposure is presumably long-term, possibly continuous, and arises from as yet unidentified carcinogens. In animal studies, different types of fiber produce widely varying results. Animal sex, strain, carcinogen dose, and other aspects of study design profoundly influence the results. Fiber in general shows no consistent protective effect. Wheat bran shows the most consistent protective effect, but even among wheat bran studies results are not completely consistent.

Human studies are just beginning to examine effects of specific types of fiber. Data currently available, however, are insufficient to conclude whether fiber itself, specific components of fiber, or some other components of diets rich in fruits, vegetables, and grains are the factors responsible for the risk reduction observed in some studies. Nor has it been established what type or amount of fiber is necessary for a protective effect. The mechanism of fiber's effects, if any, is also unknown. For all of these reasons, a specific relationship between dietary fiber and decreased risk of cancer has not been demonstrated. However, a relationship between vegetables, fruits, and grains that contain fiber and other nutrients and a reduced risk for cancer has been demonstrated.

III. Tentative Decision Not To Propose a Health Claim Relating Dietary Fiber to Decreased Risk of Cancer

FDA limited its review of the scientific evidence relating ingestion of dietary fiber and cancer to the topic of dietary fiber and risk of colorectal cancer. This limitation was deemed appropriate because the great majority of epidemiologic and intervention studies have focused on colon cancer, as have virtually all animal studies in this area. The strongest support and largest volume of evidence for a possible protective effect of fiber-rich diets is for colon and rectal cancers (colorectal cancers), the second leading causes of cancer deaths in the United States (Ref. 46). Relationships between dietary fiber and risk of cancer at other sites (for example, breast, stomach, endometrium, and ovaries) have been less extensively examined but are currently the focus of considerable research effort (Refs. 47, 30, and 25).

FDA has tentatively concluded, based on the totality of the evidence, that there is not a sufficient basis to authorize a health claim for dietary fiber and reduction in risk of cancer. Numerous human and animal studies have examined the possible role of dietary fiber intake in reducing the risk of developing colon 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 a reduced risk of colorectal cancer. Prospective epidemiologic studies are few in number and give mixed results. Animal studies indicate that certain types of dietary fiber are important in modulating the effects of chemical carcinogens.

There is substantial evidence that fiber-rich foods and diets high in fiber-rich foods, including whole grains, fruits and vegetables, are associated with reduced risk of colorectal cancer. These diets differ, however, in levels of many nutrients and in 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 sufficient to demonstrate that it is the total dietary fiber, or a specific fiber component, or specific vitamins and minerals (singly or interactively) that are related to reduction of cancer risk.

A major limitation in designing and evaluating research studies has been the need for better defined measures of dietary fiber and standardized descriptions for source, type, and amount of dietary fiber (Ref. 24). Dietary fibers are a heterogeneous family of compounds that vary considerably in chemical composition, physical characteristics, and biological effects (Refs. 12 and 24). Processing of foods and fiber sources may also alter the inherent characteristics of the fiber (Ref. 24). The commonly used analytical methodologies often do not detect many of the characteristics that vary among fibers and that may be related to biological function (e.g., particle size, chemical composition, or water-holding capacity) (Refs. 12 and 24). Analytical methods also do not differentiate between source or type of fiber. This lack of ability to detect many of the differences that exist among fibers and the general lack of clear evidence as to the mechanisms of action of fibers have raised questions as to the ability of commonly used analytical measures of dietary fiber to adequately predict biological actions of specific fibers (Refs. 12 and 24).

Another problem in evaluating the relationship of dietary fiber intakes to risk of chronic diseases such as cancer is the lack of reference food composition data on the fiber content of foods. Consequently, most human studies have described dietary intakes in terms of amounts of fruits, vegetables, or other food groups rather than as total dietary fiber intakes; or have used measures of the crude fiber content of foods rather than total dietary fiber to estimate fiber intakes. Not only do measures of crude fiber variably underestimate intakes of total dietary fiber, but they also are not necessarily reflective of the various combinations of types of fiber normally present in foods. The seriousness of this limitation varies by type and objective of study, but inappropriate and inadequate estimates of dietary fiber intakes can limit the ability to detect a fiber/cancer relationship in some studies. This limitation affects, then, the ability to link dietary fiber intakes to cancer risk.

In summary, the currently available scientific evidence is not sufficiently conclusive or specific for fiber per se to justify use of a health claim relating intake of dietary fiber to reduced risk of cancer. Federal government (Refs. 25 and 47) and other reviews by recognized scientific bodies (Refs. 24, 25, 30, and 31) are consistent in agreeing that it is difficult to separate the effects of fiber from those of other dietary components present in high fiber foods or in dietary patterns high in plant food. As noted above, the evidence that has become available since publication of these reports is consistent with these conclusions and is, therefore, not sufficient to alter the earlier conclusions. Thus, FDA has tentatively concluded, based on the totality of the scientific evidence, that there is not significant scientific agreement among experts qualified by training and experience to evaluate such a relationship, as to the independent and specific role of dietary fiber or fiber components in reducing the risk of cancer, particularly colon cancer.

Virtually all recent dietary guidelines for Americans have encouraged the increased consumption of fiber-rich foods, including whole grain cereals, fruits, and vegetables. This recommendation is also consistent with available scientific evidence which shows that changes in dietary patterns can play a significant role in reducing risk of colorectal cancer, other cancers, and other chronic diseases (Refs. 30, 47). FDA has supported and continues to support these recommendations and to encourage dietary guidance consistent with the recommendations.

This raises a dilemma, however, for which FDA is requesting comment. To encourage and help consumers to meet dietary guidance recommendations, it would be useful to have appropriate dietary information at point of purchase. The use of health claims on foods

(including dietary supplements) to inform consumers of these recommendations, however, is problematic because it is not clear what qualifying and other criteria are necessary to adequately define eligible foods for such a health claim. As described in companion documents on "General Principles for Health Claims" and in requirements for "Mandatory Nutrition Labeling," the fiber content of foods (including dietary supplements) as measured by the Association of Official Analytical Chemists method for dietary fiber is proposed to serve as the basis for nutrition labeling of fiber content and, consequently, for determining whether foods and supplements qualify for health claims. Yet as discussed above, the correspondence between analytical fiber content and biological responses is not established. Thus, health claims that derive from this basis could be misleading. Congress, in the 1990 amendments, specified that FDA evaluate nutrient and disease relationships. Dietary fiber was specified as one nutrient for evaluation. Yet, FDA has tentatively concluded that the available evidence that is supportive of food patterns containing fiber-rich foods cannot be extrapolated to a specific fiber effect at this time.

Given the public health significance of cancer, specifically colon cancer, and given the general dietary guidance to increase consumption of fruit and vegetables and whole grain products which are rich sources of dietary fiber and other nutrients, FDA is requesting comments on how to best inform consumers of these issues.

Specifically should the agency permit a claim on the label or in labeling such as: "Diets high in fruit, vegetables, whole grains are associated with a reduced risk of cancer of the lower bowel and cardiovascular disease;" or alternatively "Research has shown that populations who consume diets that contain several servings each of fruit, vegetables, and whole grains have a decreased risk of certain forms of cancer and cardiovascular disease;" or "Choose diets with plenty of fruit, vegetables, and whole grains to help lower your risk of cardiovascular disease and certain forms of cancer." If such statements should be permitted, what criteria should be used to identify foods that are eligible for such statements? For example, should such statements be limited to fresh fruit, vegetables, and milled whole grains, or should processed foods derived from these producers be also included? What measure should the agency adopt to assure that consumers are not misled as to the benefit of consuming a specific product?

The use of such claims on fruit, vegetables, and whole grains raises the issue of authority to permit claims for food as well as nutrients. FDA specifically requests comments on whether it has the authority and should allow health claims on foods as well as nutrients. FDA also requests information on how to develop regulatory criteria for such a program. If FDA were to permit such claims, what qualifying and disqualifying criteria should be used to determine eligibility for a claim, and what methods or criteria should be used for regulatory monitoring and compliance? Additionally, FDA requests comments on what criteria could be used to develop a health claim for foods that would provide truthful and not misleading messages to consumers that changes in dietary patterns are related to reductions in cancer risk.

IV. Environmental Impact

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

V. Effective Date

FDA is proposing to make these regulations effective 6 months after the publication of a final rule based on this proposal.

VI. Comments

Interested persons may, on or before February 25, 1992, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

VII. Economic Impact

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

VIII. 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.

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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 authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

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

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

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

§ 101.71 Health claims: claims not authorized.

* * * * *

(a) Dietary fiber and cancer (insert cite and date of publication in the **Federal Register** of the final rule).

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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

TABLE 1.—DIETARY FIBER AND COLORECTAL CANCER: CORRELATIONAL STUDIES

Study	Type and location	Design	Methods	Results	Comments
Rosen et al., 1988 (Ref. 37)	Correlational Sweden	Cancer mortality rates from 1969–1978 and dietary practices were studied in 24 countries.	Dietary fiber was calculated based on food expenditures for 1978. Population providing food expenditure data was a random sample of 5,760 households. All food expenditures for 2 weeks were recorded.	High intake of cereal fiber was protective against colorectal cancer for both males, females. A negative correlation between milk consumption and colorectal cancer was found.	Food eaten in restaurants and food wastage were not accounted for. Estimates were based on food expenditure rather than on consumption.
Morales Suarez-Varela et al., 1990 (Ref. 29).	Correlational, Spain	Correlated mortality rates from rectal cancer (including sigmoid colon) with dietary practices, including dietary fiber intake.	Study covered period from 1977–1965 Consumption of various diet components obtained from Natl. Statistics Institute publications. Components examined were total lipids, animal fats, vegetable fats, butter and pork lard, margarine, fiber, and alcohol.	No significant correlations were established between animal fat, vegetable fat, total lipids, or fiber and morbidity and mortality.	Data for rectal and sigmoid colon cancer were combined.

TABLE 2.—DIETARY FIBER AND COLORECTAL CANCER: CASE CONTROL STUDIES

Study	Type and Location	Subjects	Methods	Results	Comments
Benito et al., 1990 (Ref. 4).	Case control, Majorca...	286 cases of colon cancer (including rectal cancer); 295 community controls matched for age, sex; 203 hospital controls.	Subjects given food frequency questionnaire covering 6 months prior to interview.	Increased risk of colon cancer found for higher consumption of fresh meats; protection associated with high intake of cruciferous vegetables. Fourfold increase in risk of colorectal cancer found for high consumption of fresh meat, dairy products, and cereals combined with low intake of cruciferous vegetables.	The study examined effects of foods rather than fiber.
De Verdier et al., 1990 (Ref. 8).	Case control, Sweden...	452 cases of colon cancer, 268 cases of rectal cancer, 624 controls matched for age.	Dietary data obtained by food frequency questionnaire covering previous 5 years. Method of fiber calculation was not specified.	Those consuming high fiber, low protein diets had lowest risk of colorectal cancer. Fiber was protective against colon cancer for males. Fiber was protective for rectal cancer for both males and females.	Data analysis was not controlled for micronutrients or fats.
Freudenheim et al., 1990 (Ref. 9).	Case control, Western New York.	428 colon cancer cases (223 males, 205 females); 422 rectal cancer cases (145 males, 277 females); 428 community controls (223 males, 205 females).	Participants interviewed regarding frequency of consumption of foods for 1 year prior to onset of symptoms. Fiber was part of normal diet (calculated by Southgate's tables or Lanza and Butrum).	Colon cancer risk decreased with intake of grain fiber for males and females, and with fiber from fruits and vegetables for males. Insoluble grain fiber was associated with reduced cancer risk more strongly than soluble fiber. Risk of rectal cancer was reduced in those consuming more fruit or vegetable fiber but not grain fiber.	Data analysis was not controlled for micronutrients or fat.

TABLE 2.—DIETARY FIBER AND COLORECTAL CANCER: CASE CONTROL STUDIES—Continued

Study	Type and Location	Subjects	Methods	Results	Comments
Hoff et al., 1986 (Ref. 15).	Case control,	155 men and women (78 with colonic polyps and 77 without polyps.	Subjects were participating in colon polyp endoscopic screening project. They recorded food intake for 5 consecutive weekdays. Bread was analyzed, gravimetrically, for total fiber. Fiber in other dietary components estimated by use of computerized Norwegian food composition data base.	Intakes of fiber was significantly less and total carbohydrate lower in patients with large polyps vs. those without polyps. Differences in intake of cruciferous vegetables, vitamin C, animal protein were not significant. Patients with large polyps consumed significantly more fat than patients without polyps. A lower intake of vitamin C or cruciferous vegetables correlated with the presence of multiple polyps.	Individuals were unaware of their polyp status when completing dietary information, a major strength of the study. Shows a protective effect of dietary fiber and total carbohydrates. Cruciferous vegetables and vitamin C intakes were protective against multiple polyp development.
Kune et al., 1987 (Ref. 21).	Case control, Melbourne, Australia.	392 colon cancer patients; 323 rectal cancer patients 727 community controls.	Patients were identified over a 1-year period. Usual diet, covering previous 20 years, was determined by interview with dietitian. Seasonal variations in diet were accounted for. Cancer patients were interviewed postoperatively in the hospital. Nutrients analyzed for included protein, fat, fiber, energy, **β carotene and vitamin C.**	Variables not contributing to, or contributing very little to, variation in colorectal cancer risk included fats; carbohydrates; fiber from pulses, nuts, seeds; fruit; cereals; energy; retinol in the diet; meats; and milk products (not milk drinks). Combination of high fiber, high vegetable diet was protective against colorectal cancer.	Difficult to interpret interaction effects. Type of fiber (soluble vs insoluble) was not analyzed.
Lee et al., 1989 (Ref. 23).	Case control, Singapore, China.	122 colon cancer patients; 71 rectal cancer patients—all hospital based 426 controls selected from other wards of the same hospital.	Dietary intake was calculated from food frequency questionnaire, providing information of usual dietary intake one year prior to interview. Fiber intake calculated from investigator's own determinations of fiber in local foods, as well as from food composition tables.	Colon cancer: significant protective effect from cruciferous vegetables. No significant effect of dietary fiber. High meat/low vegetable intake was a risk factor. Rectal cancer: significant protective effects noted for cruciferous vegetables, total vegetables, **β-carotene, and total dietary fiber.**	Number of cases (especially of rectal cancer) was small. Cruciferous vegetable intake and a high vegetable to meat intake ratio cited as most strongly protective factors. Fiber protective only for rectal cancer.
Slattery et al., 1989 (Ref. 41).	Case control, Utah	410 colon cancer cases. Combines patient data from 2 previous studies.	Dietary data obtained by food frequency questionnaire within 6 months of diagnosis. Data collected referenced 2–5 yrs before diagnosis of colon cancer. Crude dietary fiber calculated from prediagnosis food intake. Base diet was precancer diagnosis.	Highest quartile of crude fiber intake correlated with ↑ risk of death. No clear intake response effect.	Uses crude dietary fiber.

TABLE 2.—DIETARY FIBER AND COLORECTAL CANCER: CASE CONTROL STUDIES—Continued

Study	Type and Location	Subjects	Methods	Results	Comments
Slattery et al., 1988 (Ref. 40).	Case control, Utah	231 cases of colon cancer 391 controls: 185 males & 206 females. Cases and controls were all caucasians. Controls selected by random digit dialing.	Subjects were interviewed about diet 2 years prior to diagnosis. Dietary fiber intake calculated from some direct food analyses or from tables. Values computed for neutral detergent fiber, dietary fiber, and crude fiber based on food frequency questionnaire interview.	Significant dose-response risk reduction for crude fiber in males. Weak inconsistent effect for neutral detergent fiber. No effect of dietary fiber (analyzed by method of Bitner) or grain fiber. Data for females was similar, but 95% confidence intervals included 1.0. Significant intake-response risk reduction for fruit fiber in males. Lesser effect for vegetables, no effect for grain fiber. In females, vegetables showed a significant protective effect. Fruit fiber followed a dose response but 95% confidence intervals included 1.0. Data adjusted for calorie intake age and elevated body mass index (risk factors for colon cancer in this study) and Mormon church membership.	This study is one of the few published studies that examined the effect of several analytically defined fiber fractions on colon cancer risk. Crude fiber was the fraction most strongly associated with risk reduction. The authors note that the number of cases limits the ability to be more detailed about fiber types (sugar composition, etc.) or monitor differing effects on proximal vs. distal colon.
Tuyns et al., 1987 (Ref. 44).	Case control, Belgium	818 cases of colon or rectal cancer; 2851 controls in 2 provinces of Belgium with differing dietary habits.	Patients asked about usual weekly intake for 1 week before onset of illness or at time of interview for controls. Total dietary fiber was calculated at 17.5–22.8 g/day (Southgate tables).	Significant ↓ risk of colorectal cancer with ↑ fiber consumption in both sexes and in both provinces. When adjusted for calorie intake, dose response was stronger. Also noted was a protective dose response for "polysaccharides" (starch) when adjusted for calorie intake.	Overall, showed a protective effect of total fiber.
West et al., 1989 (Ref. 48).	Case control, Utah	231 colon cancer cases: 112 males and 119 females. 391 controls: 185 males and 206 females from same community.	Food intake from subject's diets assessed by a food frequency questionnaire for the 2–3 yrs prior to interview. Fiber calculated from USDA data base and analyses of grocery foods. Data not controlled for micronutrient or fat intake.	This study reports a statistically significant ($p<0.10$) effect of crude fiber on reducing risk of colon cancer in males and females, after adjusting for age, body mass index, and energy intake. A modest intake response effect was seen for both sexes.	Apparent fiber effect may have been due to other factors in fruits and vegetables. 90% confidence intervals used in statistical analysis.
Wonlleb et al., 1990 (Ref. 50).	Case control, Arkansas.	Male VA patients: 43 with resected colorectal cancer 41 elective surgery patients.	Self administered questionnaire used to estimate approximate weekly intake of 55 food items (surveyed present diet), selected to estimate intakes of fat, fiber, vegetables, and meat. Total food consumption not recorded; did take weight and height measurement.	Study showed protective effect of wheat bran and cauliflower. Luncheon meats associated with increased risk.	Study does not examine fiber per se. Small sample size.

TABLE 3.—DIETARY FIBER AND COLORECTAL CANCER: COHORT STUDIES

Study	Type and location	Subjects	Methods	Results	Comments
Heilbrun et al., 1989 (Ref. 13).	Cohort study, records reviewed retrospectively. Hawaiian Japanese.	Subjects chosen from a group of 8,006 Hawaiian Japanese. 102 colon cancer cases; 60 rectal cancer cases.	Subjects followed for cancer occurrence for 17-20 yrs. Subjects consumed usual diet. Fiber calculated from a single 24 hr. recall taken upon entry into study in 1965-1968. Range of calculated dietary fiber intake was 1.3-43.2 g/day. Method of calculating dietary fiber not clear from text.	No effect of dietary fiber on relative risk of colon cancer in entire cohort. When group was divided in half (based on median fat intake) fiber conferred a significant protective effect only in the "low fat" half of the cohort. Vegetables/fruits also showed protective effect.	Authors consider results "preliminary" because limited #'s of cases precluded definitive analysis of fat effect. As in many other DF studies, fruits and vegetables also showed a protective effect. Only one 24 hour dietary recall (15 years before end of study) interview used to assess fiber intake. This may not accurately assess habitual diet.
Willet et al., 1990 (Ref 49).	Prospective cohort.....	88,751 subjects (female nurses, 30-55 years old) available for follow up; 150 cases of adenocarcinoma of colon.	Study of the relationships between intakes of meat, fat, and fiber and colon cancer. Follow up since 1976. Dietary questionnaire used to estimate fiber from usual diets. Used crude dietary fiber or Southgate tables.	No evidence for protective effect of crude dietary fiber on colon cancer. High intake of crude fruit fiber, but not vegetable or cereal fiber, was protective. However, adjusted for red meat consumption, the effect disappeared.	

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BILLING CODE 4160-01-M

21 CFR PART 101

[Docket No. 91N-0099]

RIN 0905-AB67

Food Labeling: Health Claims; Dietary Fiber and Cardiovascular Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing that after review of the available evidence, it tentatively finds that a basis does not exist on which to authorize the use on foods, including dietary supplements, of health claims relating to the association between dietary fiber and cardiovascular disease. While an association appears to exist between consumption of fiber-rich foods and reduced risk of cardiovascular disease, FDA tentatively finds that it cannot attribute this effect to the fiber itself. Therefore, FDA specifically requests comments on this topic. FDA has reviewed the relationship between this dietary component and this disease under the provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments).

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the 1990 amendments.

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: Joyce J. Saltsman, Center for Food Safety and Applied Nutrition (HFF-265), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-485-0316.

I. Background

A. The Nutrition Labeling and Education Act of 1990

On November 8, 1990, the President signed into law the 1990 amendments (Pub. L. 101-535), which amended the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorize the Secretary of Health and Human Services (the Secretary) to issue regulations authorizing nutrient content and health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)).

Published elsewhere in this **Federal Register** is a proposed rule to establish general requirements for health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs, or other nutritional substances (referred to generally as "substance" to a disease or health related condition on food labels and in labeling. In this companion document, FDA has tentatively determined that such claims would only be justified for substances in dietary supplements, as well as in conventional foods, if the agency determines, based on the totality of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The 1990 amendments also require (section 3(b)(1)(A)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x)) that within 12 months of their enactment, the Secretary shall issue proposed regulations to implement section 403(r) of the act (21 U.S.C. 343), and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including dietary fiber and cardiovascular disease, meet the requirements of the act.

In this document, the agency will consider whether a claim on food or