DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR part 101

[Docket No. 91N]

RIN 0905-AD08

Food labeling: Health claims and Label Statements; Dietary Fiber and Cancer

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

The Food and Drug Administration (FDA) is announcing its decision not to authorize the use on the label or labeling of foods of health claims relating to an association between dietary fiber and cancer. However, FDA is authorizing a health claim relating diets low in fat and high in fiber-containing grain products, fruits, and vegetables to a reduced risk of cancer. This action is in response to provisions of the Nutrition labeling and Education Act of 1990 (the 1990 amendments) that bear on health claims, and was developed in accordance with the final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**.

Based on the totality of the publicly available scientific evidence, including recently available evidence, the agency has concluded that there is not significant scientific agreement among qualified experts that a claim relating dietary fiber to reduced risk of cancer is supported. The publicly available evidence does indicate, however, that diets low in fat and rich in fiber-containing grain products, fruits, and vegetables are associated with a decreased risk of several types of cancer, and there is significant scientific agreement that the evidence supports this association. The evidence is not sufficient to fully explain the role of total dietary fiber, fiber components, and the multiple nutrients and other substances contained in these foods in reducing cancer risk.

EFFECTIVE DATE: May 8, 1993.

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 27, 1991 (56 FR 60556), FDA proposed to deny the use of health claims relating dietary fiber to the risk of cancer on food labeling. The proposed rule was issued in response to provisions of the 1990 amendments (Pub. L.101-535) that bear on health claims and in accordance with the proposed general requirements for health claims for food (56 FR 60537). As amended in 1990, the Federal Food, Drug, and Cosmetic Act (the act) provides that a food 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 section 403(r)(3) or 403(r)(5)(D) of the act (21 U.S.C. 343(r)(3) or 343(r)(5)(D)),

Congress enacted the health claims provisions of the 1990 amendments (Pub. L. 101-535) to help U.S. consumers maintain good health through appropriate dietary patterns and to protect consumers from unfounded health claims. Section 3(b)(1)(A) of the 1990 amendments specifically requires the agency to determine whether claims respecting 10 nutrient/disease relationships meet the requirements of section 403(r)(3) or 403(r)(5)(D) of the act. The relationship between dietary fiber and cancer is one of the claims required to be evaluated. In carrying out this inquiry, FDA limited its scientific review to the area for which the strongest scientific evidence and agreement existed: Dietary fiber and cancers of the colon and rectum (colorectal cancers).

FDA published a notice in the **Federal Register** of March 28,1991 (56 FR 12932), requesting scientific data and information on the 10 specific topic areas identified in the 1990 amendments, including dietary fiber and cancer. Relevant scientific studies and data received in response to this request were considered as part of the agency's review of the scientific literature on dietary fiber and cancer, and they were included in the proposed rule. Comments received in response to the notice and not specifically addressed in the proposed rule are summarized and addressed below.

In the proposed rule (56 FR 60566), FDA requested written comments on its tentative determination not to authorize a health claim for dietary fiber and cancer. FDA also requested comments on the following issues: (1) Should the agency permit the label or labeling of certain foods to state, for example, that diets high in fruit, vegetables, and whole grains are associated with a reduced risk of certain forms of cancer and cardiovascular disease?; (2) If such a statement were permitted, what criteria should be used to identify eligible foods? For example, should such statements be limited to fresh fruit, vegetables, and milled whole grains; or should processed foods derived from these products also be included?; (3) What measures should the agency adopt to assure that consumers are not misled as to the benefit of consuming a specific product?; (4) Does FDA have the authority to allow health claims for foods as well as nutrients?; (5) 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?; (6) 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 (56 FR at 60577)?

In addition, FDA held public hearings on January 30 and 31,1992, on all aspects of the proposed rules published in response to the 1990 amendments.

II. Summary of Comments and the Agency's Responses

The agency received approximately 100 comments (including those from the March 28,1991, request) in response to its proposed rule on health claims for dietary fiber and cancer. Comments were received from consumers, consumer advocacy groups, state health departments, organizations of health professionals, the food industry, and Government agencies.

The agency has summarized and addressed the issues raised in these comments below. Data submitted in scientific articles that were not reviewed in the proposed rule or in any of the Federal Government consensus documents or Life Sciences Research-Office (LSRO) reports are discussed in the agency's review of recent scientific evidence in section III of this document. A number of the comments received were more appropriately addressed in other documents, and these comments were forwarded to the appropriate docket for response.

A. General Comments

1. Several comments stated that there is sufficient scientific evidence to support a health claim that diets high in dietary fiber can reduce the risk of colon cancer. These comments maintained that it is well known that population groups who consume high-fiber diets have a lower incidence of cancer, and these comments cited the strength of international correlational data on per capita availability of fiber and risk of colon cancer. Other comments stated that FDA should allow a health claim regarding dietary fiber and cancer

because cancer is a major public health problem, and it is important for consumers to be well informed. Several comments stated that FDA failed to consider the rapid pace of scientific advances linking nutritional substances to the maintenance of long-term and disease prevention.

PDA agrees that cancer is a significant public health problem and is a significant cause of death. Colorectal cancers are the second and third leading causes of cancer deaths in the United States for men and women, respectively (Ref. 46). As FDA described in its proposed rule (56 FR 60566), numerous human and animal studies have examined the possible role of dietary fiber intake in reducing the risk of developing colon cancer. Most correlational studies 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, but not others, may be important in modulating the effects of chemical carcinogens.

FDA agrees that there is substantial evidence that 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 attribute the observed diet-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.

The agency disagrees with the comments that assert that international correlational data on fiber per capita availability and risk of colon cancer are sufficient to justify a health claim regarding dietary fiber and cancer. While the correlation coefficients of such studies are often large, these studies are very weak in controlling for confounding variables. Many of the countries with low incidences of colon cancer are undeveloped nations that differ in many ways from Western countries (for example, in prevalence of obesity, environmental pollution, genetic susceptibility, parasitic diseases, etc.). None of the international correlation studies reports actual food consumption; instead, each attributes consumption of fiber from averages of food disappearance. This approach does not account for food disappearance through loss or wastage (peeling, etc.) or for differing dietary habits among various socioeconomic groups within a single country. Thus, in its proposed rule, FDA tentatively found that a basis did not exist on which to authorize a health claim relating to an association between ingestion of dietary fiber and risk of cancer. In this final rule, FDA is not authorizing a dietary fiber and cancer health claim because, based on the agency's review of the scientific evidence, including scientific literature that became publicly available after the proposal's publication, and review of data in comments, the agency has concluded that the evidence is not sufficiently conclusive or specific for dietary fiber per se to justify such a health claim. The agency has concluded, however, that there is sufficient evidence to support a claim relating the ingestion of fruits, vegetables, and whole grain products to reduced risk of some cancers. These foods are also generally low in fat and are good sources of dietary fiber.

2. Several comments stated that FDA did not follow the congressional mandate to consider whether there is significant scientific agreement supporting specific health claims. The comments argued that the agency should have first identified the range of specific health claims that could be made about dietary fiber and cancer and then examined the scientific support for each claim. A related comment asserted that FDA's evaluation criteria for specific scientific studies were based on a fundamental misapprehension of its role under the 1990 amendments. The comments stated that FDA's proper role is to search the science for significant agreement, not to decide the validity of studies.

FDA disagrees with these comments. The 1990 amendments did not instruct the agency to identify the wide range of health claims that might be made with respect to the 10 topics identified and then to evaluate all published literature relevant, to the claims. Rather, the 1990 amendments instructed the agency to determine whether claims respecting the 10 areas, including "dietary fiber and cancer," meet the requirements of section 403(r)(3) or 403(r)(5)(D) of the act. The agency interpreted this directive in a straightforward and logical way. Indeed, FDA's chosen approach was necessary if the agency hoped to accomplish the congressional mandate within the prescribed timeframe and with its limited resources. Thus, FDA, in its proposed rule (56 FR 60566), focused its scientific review on those aspects of the dietary fiber and cancer relationship for which the strongest, scientific evidence exists: dietary fiber and colorectal cancer.

The agency developed its proposed rule regarding dietary fiber and cancer in conformity with the standards mandated by the 1990 amendments. FDA's role is to evaluate the totality of the publicly available scientific evidence and to assess whether there is significant scientific agreement among qualified experts that the available evidence supports the proposed claim. This evaluation necessarily involves an assessment of the validity of studies rather than merely a search for scientific agreement.

3. Several comments stated that FDA rejected health claims for dietary fiber and cancer because of rigid application of a scientific standard higher than that mandated by the 1990 amendments and that this rejection will have unfortunate public health consequences because valuable health-related information will not be transmitted to the American population.

FDA does not agree that it has applied a scientific standard higher than the one set out in section 403(r)(3)(B)(i) of the act. As required by the statute, FDA evaluated possible health claims for dietary fiber and cancer by inquiring whether, based on the totality of publicly available scientific evidence including evidence from well-designed studies), there is significant scientific agreement among qualified experts that the claim is supported. FDA is codifying the scientific standard of section 403(r)(3)(B)(i) of the act at 21 CFR 101.14(c) in the final rule on general requirements for health claims, which is published elsewhere in this **Federal Register**.

4. Several comments stated that FDA used different criteria to assess the relationship between dietary lipids and cancer and the relationship between dietary fiber and cancer.

FDA disagrees with this comment. In reviewing the scientific literature, FDA followed the standard mandated by the 1990 amendments. However, the strength and consistency of the data in these two areas led the agency to reach two different conclusions about permitting health claims.

Assessments of the relevant scientific Data, in Federal Government reports and other authoritative documents, have consistently concluded that dietary fat contributes to the risk of cancer at certain sites. In developing its proposed rule on this relationship (56 FR 60764), the agency found that new evidence was consistent with these earlier conclusions. Based on the totality of the evidence, FDA concluded that diets low

in total fat are associated with a reduced risk of some types of cancer.

In contrast, authoritative scientific documents, including Federal Government reports, have concluded that a number of components of diets rich in fruits, vegetables, and grain products contribute to their beneficial effect on cancer. For example, in its summary on dietary fiber and cancer in the National Academy of Sciences' report "Diet and Health: Implications for Reducing Chronic Disease Risk"("Diet and Health") (Ref. 30), the Committee on Diet and Health stated that "[E]ven where the evidence is strongest, it is not 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 non dietary factors (e.g., socioeconomic status)." Similarly, "Healthy People 2000: National Health Promotion and Disease Prevention Objectives" ("Healthy People 2000") (Ref. 46) notes that recommendations from the National Cancer Institute (Refs. 53 through 55), the Surgeon General's Report, the National Academy of Sciences' "Diet and Health," and "Nutrition and Your Health: Dietary Guidelines for Americans" support increased consumption of vegetables, fruits, and whole grains and cereals (Refs. 47, 30, and 45, respectively). In developing its proposed rule on dietary fiber and cancer, the agency found that new evidence did not alter these earlier conclusions. Rather, the agency found that the available scientific evidence was not sufficiently conclusive or specific for fiber per se to justify a health claim relating intake of dietary fiber alone to reduced risk of cancer.

5. Several comments stated that there were disparities in the agency's treatment of confounders, the weight given clinical studies, and emphasis on animal studies between the proposed rules on fat and cancer and on fiber and cancer. One comment stated that FDA criticized several of the fiber and cancer studies because it was not possible to separate the effects of dietary fiber from the effects of a reduced fat intake, but that the agency did not make this criticism of the fat and cancer studies.

FDA disagrees with these comments. In the fiber and cancer studies referred to in the comment, dietary fat was decreased and dietary fiber was increased; therefore, the effects could not be separated. In the majority of the fat and cancer studies, however, dietary fat was decreased and dietary fiber remained the same. Therefore, the reduction in risk of cancer observed in these studies could not have been due to an increased fiber intake.

FDA also disagrees that it relied excessively on animal studies in the fat and cancer proposal. As FDA noted in the proposed regulation on dietary fiber and colon cancer (56 FR 60566), in general, animal studies on fiber show no consistent protective effect. In contrast, animal studies on fat and cancer, taken as a whole, support a promoting effect of fat on carcinogenesis at several sites independent of the effect of energy intake. Human studies on fat are also generally supportive of a promoting effect of fat on carcinogenesis with respect to some types of cancer. The evidence on the relation between fat and cancer is further discussed in the document "Dietary Lipids and Cancer" published elsewhere in this issue of the **Federal Register**.

6. One comment stated that there are several clinical studies on fiber and few on fat and, therefore, the health claim on fiber and cancer should be approved.

FDA disagrees with this comment. The available clinical studies on fiber investigate its relationship to precursor lesions such as polyps, dysplasias, and abnormal cell morphology of the colonic epithelium, rather than to cancer itself. These studies are difficult to interpret, because at this time the actual risk factors for colorectal cancer are still incompletely understood. Moreover, it is not known how valid are markers such as secondary bile acid concentration, fecal mutagenicity, fecal weight, fecal deoxycholic acid, and activity of fecal bacterial enzymes as surrogates for the disease of colon cancer. Additional studies are needed to establish which, if any, of these factors affect the development of human colon cancer.

7. Some comments stated that FDA failed to justify its rejection of authoritative Federal Government reports (specifically, National Cancer Institute (NCI) recommendations containing the word "fiber").

FDA does not agree that, in developing its proposed rule regarding fiber and cancer, it rejected conclusions of Federal Government reports. Some comments, by citing only those portions of dietary recommendations that include the word "fiber" seek to attribute the protective effects of diets high in fruits, vegetables, and grain products to fiber per se. FDA believes that this emphasis distorts the meaning of sound dietary recommendations by failing to acknowledge the important contributions to reduced risk of disease of the wide variety of nutrients and non-nutritive substances present in diets high in fruits, vegetables, and grain products. Such an emphasis also focuses attention away from changes in overall dietary patterns and their potential contribution to reducing risk of chronic diseases.

To date, neither the Surgeon General's Report on "Nutrition and Health" (Ref. 47), the National Academy of Sciences' "Diet and Health" (Ref. 30), nor DHHS' "Healthy People 2000" (Ref. 46) has found the scientific evidence strong enough to attribute the protective effects against cancer of dietary patterns high in fruits, vegetables, and grain products solely to the fiber content of such diets. The recommendations in the Surgeon General's Report (the Report) include increased consumption of whole grain foods and cereal products, vegetables (including dried beans and peas) and fruits (Ref. 47). The Report states, "While inconclusive, some evidence also suggests that an overall increase in intake of foods high in fiber might decrease the risk for colon cancer. Among several unresolved issues is the role of various types of fiber, which differ in their effects on water-holding capacity, viscosity, bacterial fermentation, and intestinal transit time."

Similarly, the National Research Council's "Diet and Health" recommends, "Every day eat five or more servings of a combination of vegetables and fruits, especially green and yellow vegetables and citrus fruits. Also, increase intake of starches and other complex carbohydrates by eating six or more daily servings of a combination of breads, cereals, and legumes." (Ref. 30). The summary concludes:

> Studies in various parts of the world indicate that people who habitually consume a diet high in plant foods have low risks of atherosclerotic cardiovascular diseases, probably largely because such diets are usually low in animal fat and cholesterol. Some constituents of plant foods, e.g., soluble fiber and vegetable protein, may also contribute—to a lesser extent---to the lower risk of atherosclerotic cardiovascular diseases. The mechanism for the link between frequent consumption of vegetables and fruits, especially green and yellow vegetables and citrus fruits and decreased susceptibility to cancers of the lung, stomach, and large intestine is not well understood because the responsible agents in these foods and the mechanisms for their protective effect have not been fully determined. However, there is strong evidence that a low intake of carotenoids, which are present in green and yellow vegetables, contributes to an Increased risk of lung cancer. Fruits and vegetables also contain high levels of fiber, but there is no conclusive evidence that the dietary fiber itself, rather than other nutritive and non-nutritive components of these foods, exerts a protective effect against these

cancers. The Committee does not recommend the use of fiber supplements."

"Healthy People 2000" (Ref. 46) notes that recommendations from the National Cancer Institute, the Surgeon General's Report, the National Academy of Sciences' "Diet and Health," and "Dietary Guidelines for Americans" support increased consumption of vegetables, fruits, and whole grain breads and cereals "(Refs. 47, 30, and 45 respectively).

The agency's decision to prohibit the use on the label or labeling of foods of health claims relating intake of dietary fiber to decreased risk of cancer is consistent with the conclusions of Federal Government, and other authoritative reports. Moreover, the agency's determination in this final rule to authorize a health claim relating diets low in fat and high in fiber-containing grainy fruits, and vegetables to a reduced cancer risk is quite consistent with the conclusions of these reports.

8. Several comments criticized the agency for stating its review of the scientific literature with consensus documents and Government reports rather than conducting its own review of the older literature and, secondly, for focusing on the scientific evidence concerning the relationship between dietary fiber and colorectal cancer rather than on that between insoluble fiber and colorectal cancer.

FDA disagrees with these comments. In evaluating the publicly available evidence for each of the 10 health claim topics, FDA reviewed the evidence and conclusions reached in several Federal Government documents and in other reports from recognized scientific bodies (56 FR 60566). These authoritative documents represent comprehensive reviews and evaluations of the literature available at the time of their publication (generally from 1987 to 1989) and represent scientific consensus at that time. Although the reports may not have referenced a particular study described in the comment, it is improbable that the studies reviewed in the reports missed an important effect.

In preparing its proposed rule, FDA updated these reports by independently reviewing subsequently published studies. In addition, 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. The agency also reviewed and considered comments received in response to that **Federal Register** notice in developing its proposed rules. In reviewing the totality of the publicly available evidence, FDA considered studies that addressed the relationship between dietary fiber and colorectal cancer and those that addressed the relationship between insoluble fiber and colorectal cancer.

9. One comment questioned the motivation behind the agency's tentative rejection of health claims for fiber and cancer. The comment stated that the National Cancer Institute did not endorse health claims on dietary supplements, and stated that health claims for fiber should not be prohibited based on a concern that dietary supplements will be able to bear claims. Comments from supplement manufacturers asserted that, if health claims are permitted, on foods containing fiber, then fiber supplements should also be permitted to carry claims. The comment argued that there is no difference between fiber in foods and fiber in supplements and that all fiber supplements are safe, although data were not included to substantiate such a claim.

FDA does not agree that its motivation for rejecting health claims associating dietary fiber and reduced cancer risk was to prevent supplement manufacturers from making such claims. As the agency's proposal makes clear, FDA tentatively decided to deny health claims for dietary fiber and cancer because the currently available scientific evidence is not sufficiently conclusive or specific for fiber per se to justify such a claim, not because the agency wishes to preclude use of such a claim on dietary supplements.

B. Comments Regarding a Relationship Between Dietary Fiber and Cancer

10. Several comments stated that health claims for insoluble fiber, particularly grain fiber, should be allowed. Another comment stated that wheat bran and related products that affect gastrointestinal transit time and fecal weight may help prevent colon cancer when consumed with a diet low in saturated fat and high in plant foods. This comment argued that the fact that animal studies show a protective effect in the colon by fibers with bulking properties is more important than understanding the underlying mechanism. The comment stated farther that only specific fibers shown in animal studies to be protective, such as whole grain wheat, should be permitted to carry label claims.

FDA disagrees with these comments. Animal data are not consistent in showing a protective effect for insoluble dietary fiber. Indeed, corn bran, a predominantly insoluble fiber source (78 percent neutral detergent fiber), has been shown in three animal studies to enhance chemical carcinogenesis in rodents (Refs. 59, 60, and 61). While it is true that animal feeding studies using wheat bran are the most consistent in showing protective effects, animal data cannot be applied directly to humans. Taken together, the evidence for a significant role of wheat fiber in humans is still controversial. The number of human studies breaking fiber down by type (soluble, insoluble, etc.) is too small to be considered more than preliminary. Only two studies published since 1987 consider fiber type, while seven consider total fiber by source (fruit, vegetable, or grain), and five consider total dietary fiber as a single entity. The authors of a recent study state in their conclusion, "The efficacy of grain fiber in reducing the risk of colon and rectal cancer remains in question. While our results indicate some protective effect for the colon for grain fiber, most other studies do not find a grain effect" (Ref. 9). For example, the 1988 study by Slattery et al. (Ref. 40) found no effect of grain fiber.

11. Another comment provided data from an animal study that showed that wheat bran is superior to cellulose in reducing the incidence of colonic tumors in rats treated with the colonic carcinogen 1,2 dimethylhydrazine (Ref. 67). The data show that, even among insoluble fibers, differences exist in their effects on tumorigenesis. The study also showed that cellulose was more effective in reducing fecal bile acid concentrations compared to wheat bran, although this difference was apparently not statistically significant. Elevated fecal bile acid concentrations are putative risk factors for colon cancer, although in this study the cellulose group, with its lower fecal bile acid concentration, actually had significantly more colon tumors than the wheat bran group. This may further call into question the importance of dilution of fecal bile acids by fiber, a potential mechanism of action cited in this and other comments.

FDA notes that such results support its tentative conclusion in the proposed rule that fibers (even insoluble fibers) have different effects. The importance of bile acid dilution as a mechanism for effects of fiber remains to be determined.

12. One comment provided that the 1989 study by West et al. (Ref. 48), reviewed in the proposal, did control for micronutrient intake.

FDA agrees that this was incorrectly reported in the proposed rule.

13. A comment stated that the 1989 intervention study by DeCosse et al (Ref.

7) is relevant to the fiber-cancer relationship.

FDA disagrees with this comment. The patients in this study had no colons and, therefore, metabolized fiber differently and developed lesions at a different site from colon cancer patients. For these reasons, FDA believes that this study does not contribute to understanding the fiber-cancer relationship.

14. A comment cited the study of Rosen et al. (Ref. 37) to support the role of grains in reducing the risk of colon cancer.

FDA disagrees with this comment. The comment did not mention that the referenced study examined mortality data from 1969 to 1978 and surveyed food expenditures for 1978 only. Thus, the individuals who died of colon cancer had been dead for up to 10 years when the food expenditure data was collected. It is a weakness of this study that only a single year's food survey (1978) data were used, while mortality figures from the previous 10 years are incorporated. It is possible that this type of food data collection would accurately reflect the diet of the group which died from colon cancer up to 10 years earlier.

15. Several comments stated that studies with statistically insignificant but generally favorable results should be regarded as supportive of the relationship between fiber and cancer risk reduction.

FDA disagrees with this comment. Lack of statistical significance indicates that such findings could have arisen by chance and thus cannot be used to support a causal relationship.

16. One comment stated that overestimation of fiber intake (by inaccurate dietary or analytical methods) will result in underestimation of risk reduction.

FDA disagrees with this comment. Fiber consumption may be overestimated by a consistent factor in both the control and cancer groups. Such overestimation would have the effect of multiplying the intake of both groups by a common factor; for example, it could increase the intake in both groups by 30 percent. The differences between groups would also be multiplied by this common factor, and should be no less readily apparent than without this factor of overestimation, provided fiber intake is overestimated in each group to the same extent. Only if fiber intake were consistently overestimated in the cancer group, but not in the control group, would there be an apparent reduction of a protective effect. Because the same survey and analytical methods were applied to both groups, this seems an unlikely occurrence.

FDA recognizes that imprecise measures of fiber intake will usually tend to reduce associations between fiber intake and risk. Imprecise measurements do not necessarily result In overestimation of fiber, but merely inaccuracy in reporting the fiber content of certain foods. Lack of accuracy will hinder demonstration of a true relationship if one indeed exists between fiber and colon cancer risk reduction.

17. One comment noted that lack of a known mechanism of action for the putative effects of fiber in colon cancer risk reduction should not prevent the acceptance of claims of fiber's usefulness for this purpose. The comment made an analogy to drugs, arguing that they are often approved simply on evidence of efficacy, without clear knowledge of their mechanism of action.

FDA does not believe that the comparison to drug approval is apt. Drugs are substances of known chemical composition. In contrast, it is not known what fiber component or components may be responsible for the effects observed in some epidemiological studies. Fiber is a complex mixture of cellulose, hemicellulose, pectic substances, or other polysaccharides. Some of these materials, when isolated, have been found to promote rather than inhibit chemical carcinogenesis in rodents. Certainly it has not been established which of the components (all of which are types of "fiber") may reduce the risk of colon cancer in humans. Thus, more is at issue here than the mechanism of action; the identity of the actual active agent, if any, is also obscure.

18. One comment noted that fat and fiber intake correlate inversely with one another in many studies, and that this correlation is often statistically significant.

FDA notes that correlations between two dietary variables within a study do not demonstrate that either is causally related to the study endpoint (cancer). Rather, the two measures are merely associated with one another, in such a way that when one increases, the other decreases, and vice versa. Therefore, such a finding does not imply that increased fiber intake is causally related to decreased cancer incidence.

19. A comment noted that increasing fiber intake may promote decreased energy intake and that adding fiber in purified form to foods is not known to be harmful. The comment cited a 13-week study of oat hull feeding in rats as support.

FDA disagrees with this comment and notes that decreased energy intake in response to high fiber intake has not been shown consistently in all animal studies in which fiber-fed groups generally had similar body weights compared to no-fiber groups. FDA also disagrees with the broad statement that adding purified fiber to foods is not known to be harmful. A 13-week study dealing with one specific type of fiber is not sufficiently long to address chronic safety issues about all types of fiber. Nor were the full battery of toxicological endpoints customarily examined in safety evaluations performed in this study.

C. Food Claims Versus Nutrient Claims

In its proposed rule. FDA specifically requested comments on how best to inform consumers of the general dietary guidance to increase consumption of fruits, vegetables, and whole grain products that are rich sources of dietary fiber and other nutrients. In response to this request, FDA received a wide range of comments expressing strong support for health claims for foods rather than only for specific nutrients. National cancer research and health organizations, consumers, and consumer advocacy groups recommended allowing claims for whole foods. Several comments from the food industry also supported health claims for whole foods. These comments are summarized below.

20. Many comments supporting health claims for foods recommended that only those foods high in fiber should be permitted to carry a claim and that claims should not be allowed if they give the impression that dietary fiber, as a single nutrient, is responsible for the reduction in cancer risk associated with diets high in fruits, vegetables, and grain products.

FDA agrees with this comment that a health claim should not give the impression that a single nutrient is responsible for the reduction in cancer risk. Where the evidence is strongest, it is not possible to separate the effects of fiber from those of other components of the diet, such as fat, total calories, and vitamins.

21. Another comment stated that because the public is advised to increase its daily intake of dietary fiber. FDA should "exert control where it is needed" to avoid abusive use of fiber in foods and supplements. The comment stated that specific foods (e.g., no-fiber foods to which fiber is added) and fiber supplements should not be allowed to bear health claims.

FDA has determined that a health claim relating dietary fiber to cancer is

not supported by the totality of the publicly available scientific evidence. The claim that the agency is authorizing deals instead with diets high in fruits, vegetables, and grain products and may be carried by fruits, vegetables, and grain products that, without fortification, qualify as "good sources" of dietary fiber. This claim respects the states of the scientific evidence; it does not represent a position that other foods, including supplements, may not be able to bear a fiber/cancer claim in the future, should appropriate evidence demonstrating the validity of such a claim, be brought to the agency's attention.

22. Other comments supported narrowly worded statements concerning overall diets and their effect on risk of cancer.

FDA agrees with this comment that a health claim, as outlined in the final rule, "Labeling; General Requirements for Health Claims for Food," should be stated in context of the total diet. Certain statements about overall diets and their effects on disease or health-related conditions would be considered dietary guidance and not regulated as health claims. In this rule, FDA is authorizing a reference to certain substances (fat and fiber) as part of a statement relating diets high in fruits, vegetables, and grain products to cancer risk.

23. Some comments stated that, if claims are allowed for fiber-containing foods, the fat content should be disclosed on the label.

FDA shares the comments' concern about, the fat content of foods bearing the authorized claim. For a food to qualify for a health claim under § 101.76, it must meet the requirements for a "low fat" food as defined under §101.62.

24. Some comments provided recommendations for developing regulatory criteria. For example, several comments stated that all foods, whether fresh or processed, should meet the game standards. Other comments stated that fiber-only products should be carefully evaluated to ensure that they qualify as foods according to criteria defined in the proposed regulations.

FDA notes new § 101.76(c)(2)(ii) contains the criteria that food must meet to qualify for the authorized health claim. A food must be or contain a fruit, vegetable, or grain product must be "low fat;" and must be a "good source" of fiber.

25. Several comments noted that FDA acknowledges that virtually all dietary guidelines for Americans have encouraged consumption of fiber-rich foods, including whole gram cereals, fruits, and vegetables, and that comprehensive government reviews and other reviews by recognized scientific bodies have concluded that dietary patterns that include fiber-rich foods are associated with reduced risk of colorectal cancer, coronary heart disease, and other chronic diseases. The comment asserted that FDA should authorize the use of health claims for the relationship between dietary fiber and cancer.

FDA disagrees that the evidence is sufficient to support a claim that dietary fiber, as a single nutrient, is responsible for the reduction in cancer risk. However, FDA is authorizing a claim relating diets high in fiber-containing grain products, fruits, and vegetables to reduced cancer risk.

26. The American Cancer Society commented that it is unclear what aspect of fiber-rich foods reduces the risk of colorectal cancer. According to the American Cancer Society, the evidence does show, however, that fiber-rich diets reduce the risk of cancer, In its nutrition guidelines, the Society recommends, that people "eat more high fiber foods, such as whole grain cereals, legumes, vegetables, and fruits." This recommendation emphasizes the importance of the total diet rather than individual components of it. The American Cancer Society recommended the use of a general food claim at the point of purchase that does not mention fiber or specific cancer sites. The comment stated further that, although the American Cancer Society does refer to the cancer prevention possibilities of fiber-rich foods in its educational materials, the American Cancer Society does not think this reference should be stated on food labels, because it is still unclear which qualities of such foods actually reduce cancer risk. For example, many fiber-rich foods are also low in fat and high in antioxidant vitamins. The American Cancer Society believes that if a claim is allowed, it should not be used on food labels unless the food meets the requirements for a "high fiber" nutrient content claim.

The National Cancer Institute supports, the use of health claims on whole foods and diets high in fiber-containing foods and low in fat. Their comment stated that there is substantial and sufficient evidence that consumption of diets high in fruits, vegetables, and cereal grains are associated with the reduced risk of some types of cancer, particularly colorectal cancer. The National Cancer Institute recommended that the statement "high fiber diets" or some similar term be included in the label claim. In contrast to the American Cancer Society, the National Cancer Institute also recommended that only foods that contain naturally occurring fiber be allowed to carry a claim relating consumption of vegetables, fruits, and grain products to reduced risk of cancer. The comment stated that there is no agreement among scientific experts that fiber from fortified foods and supplements has a similar protective effect. In addition, the National Cancer Institute expressed safety concerns relative to the consumption of amounts of fiber from a single dietary source.

FDA agrees that dietary patterns with higher intakes of vegetables (including legumes), fruits, and whole grains are associated with a reduced risk of some types of cancer (see Refs. 15, and 21 through 23 in the proposed rule (56 FR 60566) and Ref. 56 in this document). Although the specific roles of the numerous potentially protective substances in plant foods are not yet understood, populations with diets rich in these foods experience many health advantages, including lower rates of some cancers. Currently, there is not scientific agreement about whether the observed protective effects against cancer are due to a combination of the nutrient components of the foods, including fiber, to other components of the diet (for example, minerals, vitamins, etc.), or to displacement of other foods in fiber-rich diets (for example, replacement of meats, fats). Rather, the evidence currently demonstrates that it is the dietary pattern, and not a single nutrient, that is important in the reduction in risk of diseases such as cancer. If the scientific evidence were sufficient to support a health claim regarding the relationship between dietary fiber and cancer, no distinction would be made between "naturally occurring" fiber and fiber supplements. The final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**, treats dietary supplements, and conventional foods consistently.

III. Review of the Recent Scientific Evidence

A. Human Studies

FDA has reviewed studies that became publicly available after the publication of its proposed rule and data submitted as comments. These studies are summarized in Table 1.

A case control study by Soltero et al. (Ref. 56) in Puerto Rico focused on prior cholecystectomy as a risk factor for right-sided colon cancer. A food frequency questionnaire was also

administered to the subjects (or next of kin, if subjects were deceased). Cholecystectomy was confirmed to be a significant risk factor for right-sided colon cancer. Subjects with cancer reported consumption of significantly more meat and poultry and less fiber (as crude fiber) and vegetables than controls. Differences in fat intake were not statistically significant. It was not clear from the report if fiber included all sources of fiber or only cereal fiber. A protective effect was also seen for vegetables: it cannot be determined whether the effect reported for fiber was due to fiber itself or to other nutrient constituents of fiber-containing foods.

Giovannucci et al. (Ref. 62) studied a cohort of 49,296 U.S. health professionals, 40 to 75 years of age, for 2 years. The authors recorded diet by questionnaire and assessed colonic adenoma incidence based on sigmoidoscopy biopsy reports. Intake of animal fat was found to be positively associated with polyp incidence. Fiber from either fruits, vegetables, or grains were all significantly protective, whether measured as crude fiber or dietary fiber. Vegetable-associated nutrients (potassium, B-carotene, vitamins C and E) were also protective, but in a combined statistical analysis they did not account for the independent effect of fiber. Three factors limit the applicability of these findings. (1) The total fat intake of most of the subjects was low by general population standards; (2) right-sided lesions in the colon were not considered, and therefore no conclusions can be drawn about right-sided colon cancer from these data; and (3) all of the study subjects were men. A large cohort study involving U.S. nurses, the majority of whom were female, published in 1990, showed no protective effect of fiber or its components on colon cancer (Ref. 49). Giovannucci et al. do not address the differences between these two studies.

Kune et al. (Ref. 63) studied dietary factors in a case-control study of colonic polyp patients. Forty-nine patients with histologically confirmed colonic polyps (greater than 1 centimeter in size) were interviewed about their dietary practices from the previous 20 years. Interview results were compared with those of 727 community controls. Consumption of fiber and vegetables was associated with a significantly reduced relative risk (in both sexes) of polyps, while consumption of milk, beef, and beer were all associated with significantly increased risk (in males only). The study combines fiber and vegetable consumption, making it difficult to assess any independent role of fiber. Micronutrient intake from vegetables (except vitamin C), exercise, and total energy intake are potential confounding variables that were not controlled.

Gregoire et al. (Ret. 64) examined rectal cell proliferation, fecal bile acid concentration, and fecal pH in a 5-day feeding study in normal, healthy volunteers. Groups of 10 or 11 subjects consumed either a low fat/low fiber, low fat/high fiber, high fat/low fiber, or high fat/high fiber diet. Fiber was derived from a bread containing 43 percent wheat bran, 45 percent wheat flour, and 2 percent gum tragacanth as fiber sources. Approximately 41 grams (g) per (/) day of fiber were consumed in the high-fiber groups, versus 6 to 7 g/day in low fiber groups. Statistical analysis for main effects of fiber on labeling index, fecal pH. and fecal bile acid concentration revealed no statistically significant effects.

Entry of fiber into the colon influences short-chain fatty acid production. Cell culture studies have suggested that altered concentrations of short-chain fatty acids within the colon may influence colonic carcinogenesis. Butyrate production may be especially protective. Clausen et al. (Ref. 65) studied fecal short-chain fatty acid composition in 16 controls, 17 patients with resected adenomatous polyps, and 17 patients with resected colonic cancer. An analysis of fresh feces from the three groups revealed no significant differences in types or relative amounts of fecal short-chain fatty acids. Feces were also incubated in vitro for 6 to 24 hours with added boluses of wheat bran or psyllium. Under these conditions, relatively less butyrate was produced by inocula from adenoma and carcinoma patients. The authors propose that reduced butyrate production in patients may be of significance in the etiology of the neoplasms, although the butyrate content of the feces from cases was similar to that of control subjects when not incubated in vitro. It cannot be determined whether the same effects in the in vitro incubations would occur in vivo if the subjects were fed wheat bran or psyllium. The role of butyrate and other short-chain fatty acids in human colon carcinogenesis has not been clearly established.

McGarrity et al. (Ref. 66) studied the effects of fat and cellulose fiber on the growth and biochemical characteristics of two human colon cancer cell lines implanted subcutaneously in nude mice. Mice received either a low fat/low fiber diet. a high fat/low fiber diet, or a high fat/high fiber diet. The added cellulose tended to eliminate the growth-enhancing properties of a high fat diet, but the effects were not statistically significant. Differences in weight gain among the different groups at least partially explained the differences in tumor growth observed. Results with implanted tumors at a noncolonic site cannot be directly generalized to spontaneous colon tumors, which are exposed to the colonic contents as well as to the systemic blood supply.

Reduced fecal bile acid content is thought to be a beneficial factor for colon cancer risk. One comment described preliminary results of a human dietary intervention study (Ref. 58) in this area that has not yet been published. In this study, female subjects consumed wheat, corn, or oat bran supplements in addition to their usual diets. Fecal bile acids, neutral sterols, and fecal enzymatic activities of enzymes that produce fecal mutagens or carcinogens were measured before and after the intervention. Wheat bran supplementation reduced the activity of all four "risk factor" enzymes studied, while oat bran produced significant reductions in three of four enzymes, and corn bran produced significant reductions in only two of four. Alterations in stool weight are probably responsible for some of these changes. Wheat bran supplementation significantly reduced total and secondary bile acid concentration in feces, while oat bran and corn bran did not.

B. Conclusions From New Studies

These additional studies provide further data on the possible link between consumption of dietary fiber consumption and reduced risk of colon cancer. With the exception of the study by Giovanucci et al. (Ref. 62), none of the studies provides evidence of an independent contribution of fiber itself (distinct from its presence in food) to risk reduction. Rather, the studies show a relationship between diets rich in fiber-containing foods and reduced risk of cancer. The Giovannucci et al. study is limited in its applicability, however, as only lesions of the descending colon were considered, and the subjects were men who already consumed a diet lower in fat and higher in vegetables than a typical U.S. diet.

The preliminary results of Reddy's study (Ret 58) on the effects of amount and type of dietary fiber on colonic bacterial enzymes and bile acids in humans support FDA's observations that insoluble fiber has not consistently been shown to be the protective fiber fraction. Wheat bran and corn bran (both largely insoluble fibers) exerted opposite effects in this risk factor study, as they do in most published animal

carcinogenesis studies. It must also be noted that the risk factors measured in this study have only postulated significance in the etiology of human colon cancer at the present time.

Although the current scientific evidence does not support a specific health claim for dietary fiber and reduced risk of cancer, the data do support a relationship between diets high in fiber-rich foods and low in fat and a reduced risk of some forms of cancer. Therefore, as discussed below, FDA will allow a health claim on vegetables, fruits, and, grain products relating diets high in these foods to a reduced risk of cancer, and specifying that these foods contain dietary fiber.

IV. Decision to Deny a Health Claim Relating Dietary Fiber to a Reduced Risk of Cancer

Overall, the currently available scientific evidence is not sufficiently conclusive or specific for fiber per se to justify use of a health claim relating the intake of dietary fiber to a reduced risk of cancer. 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. Commonly used analytical methodologies do not detect many of the characteristics that may vary among fibers and that may be related to biological function (e.g., particle size, chemical composition, water-holding capacity). The inability to detect many of the differences among fibers and the general lack of clear evidence as to the mechanisms of action of fibers raise questions about the ability of commonly used analytical measures of dietary fiber to adequately predict biological actions of specific fibers. Therefore, for these reasons, new § 101.71(a) is added to reflect FDA's decision not to authorize use of a health claim relating dietary fiber to a decreased risk of cancer.

FDA's decision is consistent with recent recommendations in the Institute of Medicine's report "Nutrition Labeling: Issues and Directions for the 1990s" (Ref. 57). This report notes that there has been great interest in the specific effects of dietary fiber on several chronic diseases. According to the report the strongest argument for an increased consumption of dietary fiber is the important contribution it makes to normal bowel function. Clear scientific associations of fiber intake with the incidence of cancer have not been made. The report indicates that one reason for this may be the difficulty in designing appropriate experiments to test specifically for the effect of dietary fiber. Foods high in dietary fiber are also generally low in calories and total and saturated fatty acids and devoid of cholesterol; thus, determination of a specific fiber effect in a feeding study is difficult. Moreover, according to the report, foods have a variety of fiber components and each may have different actions. Chemically and physiologically, cellulose, lignin, hemicellulose, pectin and alginate (all relatively purified fiber types) behave differently. Wheat bran, oat bran, and rice bran (all heterogeneous mixtures of fibers) are not similar in composition. It is also very difficult to analyze dietary fiber chemically, and thus it is hard to correlate the role of specific fiber components to health effects (Refs. 30 and 57).

Therefore, FDA is not authorizing the use on the labels and labeling of foods of health claims relating to an association between the ingestion of dietary fiber and a reduction in the risk of cancer. In reaching this decision, the agency considered all comments received in response to its proposed rule (56 FR 60566), and reviewed the scientific literature that became publicly available after the proposal's publication and data submitted with comments.

V. Decision to Allow a Health Claim on Foods Relating Diets Low in Fat and High in Fiber-Containing Grain Products, Fruits, and Vegetables to a Reduced Risk of Cancer

FDA has reviewed numerous authoritative documents, including Federal Government reports, as well as recent research on dietary fiber and cancer risk. In addition, the agency considered all comments received in response to its proposed rule. The agency has concluded that the publicly available scientific evidence supports an association between diets low in fat and high in fiber-containing grain products, fruits, and vegetables and reduced risk of cancer.

FDA agrees with the comments that argue that dietary patterns that are low in fat and high in fiber-containing grain products, fruits, and vegetables (including legumes}, are associated with a decreased risk of some types of cancer. Although the specific role of total dietary fiber, fiber components, and the multiple nutrients and other substances contained in these foods are not yet fully understood, many studies have shown, that diets high in fiber-containing foods are associated with reduced risk of some types of cancer.

Thus, the conclusion that diets low in fat and high in fiber-containing grain products, fruits, and vegetables, foods also generally low in fat, are associated with a reduced risk of cancer is consistent with the available scientific evidence. As discussed in the final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**, statements about good nutrition that do not expressly or by implication refer to a substance are considered dietary guidance and not health claims. In this rule, FDA is authorizing the inclusion of a reference to dietary fiber in a statement about the value of grain products, fruits, and vegetables in reducing cancer risk. Thus, the health claim permitted under this regulation to be used on the label or labeling of certain foods associates diets low in fat and high in fiber-containing grain products, vegetables, and fruits with a reduced risk of some cancers.

VI. Description of and Rationale for Components of the Health Claim.

A. Relationship and Significance Statements

In new § 101.76(a), the summary of the relationship between diets high in fiber-containing grain products, fruits, and vegetables and reduced cancer risk is consistent with the conclusions reached in the review of the scientific evidence. It is not known whether it is fiber, per se, or some other substance in fruits, vegetables, and grain products that functions as the protective agents or, if it is fiber, what types and characteristics of the heterogeneous family of fiber compounds are most beneficial. Yet, because of the usefulness of dietary fiber in identifying the types of foods most likely to correlate with reduced cancer risk, fiber is specifically identified as being characteristic of the protective dietary pattern. Thus fiber can serve as the identifying marker. Other components of the relationship statement, for example, risk factors, have been indicated, as in other authorized health claims.

New § 101.76(b), on the significance of the relationship between consumption of diets low in fat and high in fiber-containing grain products, fruits, and vegetables and reduced risk of cancer, includes the information that U.S. diets tend to be high in fat and low in grains, fruits, and vegetables. A discussion of current dietary guidelines on recommended servings of grain products, fruits, and vegetables is also provided.

B. Nature of the Claim

In new § 101.76(c)(2)(i), FDA is authorizing a health claim relating

substances in diets low in fat and high in fiber-containing grain products, fruits, and vegetables to reduced risk of cancer. ln new § 1011.76(c)(2)(i)(A), the agency is requiring, consistent with other authorized claims, that the relationship be qualified with the terms "may" or "might." These terms are used to indicate that not all persons can necessarily expect to benefit from these dietary changes.

In new § 101.76(c)(2)(i)(B), the agency, consistent with other authorized claims, is requiring that the claim not indicate that all cancers may be affected, but rather that the risk of "some types of cancer" or "some cancers" may be reduced. The relationship between dietary factors and various types of cancers is variable; in many cases, the available data are inadequate to specifically identify which cancers may be affected.

In new § 101.76(c)(2)(i)(C), the agency is requiring that the claim be limited to grain products, fruits, and vegetables that contain dietary fiber. As noted in the conclusions reached from the available scientific evidence, it is not known what fiber substance or other substances in grain products, fruits, and vegetables are responsible for their protective effect. A role for dietary fiber has been hypothesized and has biological plausibility. Intakes of fiber and other nutrients from grains, fruits, and vegetables are correlated with reduced cancer risk. By requiring that the characterizing nutrient be identified as characteristic of a dietary pattern rich in fiber-containing grains, fruits, and vegetables, without specifically attributing the cause to a nutrient, the claim is more consistent with the current scientific knowledge. The claim should also minimize consumer confusion, because its wording is similar to current dietary guidelines from the U.S. Government, including the National Cancer Institute.

New § 101.76(c)(2)(i)(D) requires that health claims indicate that development of cancer depends on many factors. This requirement is intended to prevent consumers from being misled that grain product, fruit, and vegetable intake is the only factor connected with cancer risk. In new § 101.76(c)(2)(i)(E), FDA, consistent with other authorized health claims, is prohibiting the attribution of a specific reduction in risk of cancer to diets low in fat and high in fiber-containing grain products, fruits, and vegetables. In new § 101.76(c)(2)(i)(F) and (c)(2)(i)(G), FDA is prohibiting, consistent with other authorized health claims, more specific use of dietary terms than is warranted by the current state of the scientific evidence. These requirements also standardize use of these terms, thus minimizing consumer confusion as they compare food labels across products, or as they compare a health claim to the nutrition information panel.

C. Nature of the Food

New § 101.76(c)(2)(ii)(A) requires that the food bearing the health claim be or contain a grain product, fruit, or vegetable. Because the claim relates to diets high in these foods, it. would not make sense for it to appear on the labeling of another type of food. A health claim that appears on a food that meets all the requirements in § 101.76(c)(2)(ii), but contains only a trivial amount of grain product, fruit, or vegetable, could be considered misleading and might misbrand the food under section 403(a) of the act. FDA, consistent with the requirements for the health claim on dietary fat and cancer (published elsewhere in this issue of the **Federal Register**), is requiring in new § 101.76(c)(2)(ii)(B) that foods bearing the health claim be "low fat" foods, or alternatively, belong to a class of products that is "low in fat." Low fat diets are associated with reduced cancer risks. Low or negligible fat is also one of the characterizing features of diets rich in grain products, fruits, and vegetables. Because the effect of fat is not readily separated from the effect of other nutritive components of grain products, fruits, and vegetables, it is being made a qualifying nutrient.

In new § 101.76(c)(2)(ii)(C), FDA is requiring that. grains, fruits, and vegetables, bearing the authorized health claim qualify as e "good source" (greater than or equal to 10 percent of the daily reference value (DRV)) for dietary fiber. The requirement that these foods contain 10 percent of the DRV for dietary fiber is being set as a specific alternate to the 20 percent (i.e., "high") requirement, for qualifying nutrients in the final rule on general requirements for health claims, published elsewhere in this **Federal Register**. This alternate level was deemed useful to assure that most grain products, fruits, and vegetables, would be eligible for this health claim, because these foods in general have been correlated with reduced cancer risk, and because they are significant sources of dietary fiber in the U.S. dietary pattern. Without this alternative level, very few grain products, fruits, and vegetables, would qualify for the health claim, which would be contrary to the available scientific evidence and to the purpose of health claims.

This section also requires that foods qualify as a good source of fiber based on their natural level of fiber. This means that foods which require fortification with dietary fiber, in order to meet the qualifying criteria for the health claim, cannot bear the claim. This requirement is consistent with the scientific basis for the claim, that is, that grains, fruits, and vegetables, in their native form correlate with reduced cancer risk. Because there are not sufficient data that specifically identify dietary fiber, or particular components of fiber, as causal and because this nutrient is being used as a marker for the substance or substances in grain products, fruits, and vegetables, that provide the observed protective effect, it is the native composition of the foods that identifies their usefulness. At the same time, this requirement does not prohibit fortification of qualifying foods with dietary fiber, once the qualifying level has been met naturally.

D. Optional Information

Under new § 101.76(d), similarly to other authorized health claims, health claims may identify additional risk factors for cancer. The regulation specifies the factors that may be listed; all are risk factors about which there is general scientific agreement. This additional information can provide a context that is useful for an understanding of the relationship of the diet to the disease, but manufacturers are cautioned that it should not be presented in a way that is misleading to the consumer. A health claim may also indicate that reductions in fat intake and consumption of fruits, vegetables, and grain products are part of a total dietary pattern that is consistent with the latest "Nutrition and Your Health: Dietary Guidelines for Americans," published jointly by the U.S Department of Agriculture and the U.S. Department of Health and Human Services (Ref. 45). Consistent with other health claim regulations, the claim may also include information on the prevalence of cancer in the United States. In order to ensure that this information is valid, the agency is requiring that it come from one of three specified authoritative sources.

E. Model Health Claims

In new § 101.76(e) FDA is providing several model health claims to illustrate the requirements of new § 101.76. FDA is not prescribing specific language for claims, but certain elements are required, and these models include the required elements.

VII. 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.

VIII. Economic Impact

In its food labeling proposals of November 27, 1991 (58 FR 60366 et seq), FDA stated that the food labeling reform initiative, taken as a whole, would have associated costs in excess of the $100 million threshold that defines a major rule. Thus, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA developed one comprehensive regulatory impact analysis (RIA) that presented the costs and benefits of all of the food labeling provisions taken together. That RIA was published in the **Federal Register** of November 27, 1991 (56 FR 60856), and along with the food labeling proposals, the agency requested comments on the RIA.

FDA has evaluated more than 300 comments that it received in response to the November 1991 RIA. FDA's discussion of these comments is contained in the agency's final RIA published elsewhere in this issue of the **Federal Register**. In addition, FDA will prepare a final regulatory flexibility analysis (RFA) subsequent to the publication of the food labeling final rules. The final RFA will be placed on file with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, and a notice will be published in the **Federal Register** announcing its availability.

In the final RIA, FDA has concluded, based on its review of available data and comments, that the overall food labeling reform initiative constitutes a major rule as defined by Executive Order 12291. Further, the agency has concluded that although the costs of complying with the new food labeling requirements are substantial, such costs are outweighed by the public health benefits that will be realized through the use of improved nutrition information provided by food labeling.

IX. References

The following references have been placed on file 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, 21 CFR part 101 is amended as follows:

PART 101-FOOD LABELING

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

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

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

§101.71 Health claims: claims not authorized.

* * * * *

(a) Dietary fiber and cancer.

3. New § 101.76 is added to subpart E to read as follows:

§ 101.76 Health claims: fiber-containing grain products, fruits, and vegetables and cancer.

(a) *Relationship between diets low in fat and high in fiber containing grain products, fruits, and vegetables and cancer risk*. (1) Cancer is a constellation of more than 100 different diseases, each characterized by the uncontrolled growth and spread of abnormal cells. Cancer has many causes and stages in its development. Both genetic and environmental risk factors may affect the risk of cancer. Risk factors include: A family history of a specific type of cancer, cigarette smoking, overweight and obesity, alcohol consumption, ultraviolet or ionizing radiation, exposure to cancer-causing chemicals, and dietary factors.

(2) The scientific evidence establishes that diets low in fat and high in fiber-containing grain products, fruits, and vegetables are associated with a reduced risk of some types of cancer. Although the specific role of total dietary fiber, fiber components, and the multiple nutrients and other substances contained in these foods are not yet fully understood, many studies have shown that diets low in fat and high in fiber-containing foods are associated with reduced risk of some types of cancer.

(b) *Significance of the relationship between consumption of diets low in fat and high m fiber-containing grain products, fruits, and vegetables and risk of cancer*. (1) Cancer is ranked as a leading cause of death in the United States. The overall economic costs of cancer, including direct health care costs and losses due to morbidity and mortality, are very high.

(2) U.S. diets tend to be high in fat and low in grain products, fruits, and vegetables. Studies in various parts of the world indicate that populations who habitually consume a diet high in plant foods have lower risks of some cancers. These diets generally are low in fat and rich in many nutrients, including, but not limited to, dietary fiber. Current dietary guidelines from Federal government agencies and nationally recognized health professional organizations recommend decreased consumption of fats (less than 30 percent of calories), maintenance of desirable body weight, and increased consumption of fruits and vegetables (five or more servings daily), and grain products (six or more servings daily).

(c) *Requirements*. (1) All requirements set forth in § 101.14 shall be met.

(2) Specific requirements. (i) *Nature of the claim*. A health claim associating diets low in fat and high in fiber-containing grain products, fruits, and vegetables with reduced risk of cancer may be made on the label or labeling of a food described in paragraph (c)(2)(ii) of this section, provided that:

(A) The claim states that diets low in fat and high in fiber-containing grain products, fruits, and vegetables "may" or "might" reduce the risk of some cancers;

(B) In specifying the disease, the claim uses the following terms: "some types of cancer," or "some cancers";

(C) The claim is limited to grain products, fruits, and vegetables that contain dietary fiber;

(D) The claim indicates that development of cancer depends on many factors;

(E) The claim does not attribute any degree of cancer risk reduction to diets low in fat and high in fiber-containing grain products, fruits, and vegetables;

(F) In specifying the dietary fiber component of the labeled food, the claim uses the term "fiber", "dietary fiber" or "total dietary fiber"; and

(G) The claim does not specify types of dietary fiber that may be related to risk of cancer.

(ii) *Nature of the food*. (A) The food shall be or shall contain a grain product, fruit, or vegetable.

(B) The food shall meet the nutrient content requirements of § 101.62 for a "low fat" food.

(C) The food shall meet, without fortification, the nutrient content requirements of § 101.54 for a "good source" of dietary fiber.

(d) *Optional information*. (1) The claim may include information from paragraphs (a) and (b) of this section, which summarize the relationship between diets low in fat and high in fiber-containing grain products, fruits, and vegetables, and some types of cancer and the significance of the relationship.

(2) The claim may identify one or more of the following risk factors for development of cancer: Family history of a specific type of cancer, cigarette smoking, overweight and obesity, alcohol consumption, ultraviolet or ionizing radiation, exposure to cancer causing chemicals, and dietary factors.

(3) The claim may indicate that it is consistent with "Nutrition and Your Health: Dietary Guidelines for Americans," U.S. Department of Agriculture (USDA) and Department of Health and Human Services (DHHS), Government Printing Office.

(4) The claim may include information on the number of people in the United States who have cancer. The sources of this information must be identified, and it must be current information from the National Center for Health Statistics, the National Institutes of Health, or "Nutrition and Your Health: Dietary Guidelines for Americans," USDA and DHHS, Government Printing Office.

(e) *Model health claims*. The following-model health claims may be used in food labeling to characterize the relationship between diets low in fat and high in fiber-containing grain products, fruits, and vegetables and cancer risk:

(1) Low fat diets rich in fiber-containing grain products, fruits, and vegetables may reduce the risk of some types of cancer, a disease associated with many factors.

(2) Development of cancer depends on many factors. Eating a diet low in fat and high in grain products, fruits, and vegetables that contain dietary fiber may reduce your risk of some cancers.

Dated: November 3, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Luis W. Sullivan,

Secretly of Health and Human Services.

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

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TABLE
DIETARY FIBER AND CANCER

Study	Study Design	Subjects	Methods	Results	Comments
Kune, et al., 1991 (Ref. 63)	Case-control	Cases: 49 patients who had one or more histologically confirmed adenomatous polyp larger than 1 cm in diameter removed by endoscopy. Controls: 727 community controls.	50 patients from Melbourne, Australia, who had histologically confirmed adenomatous polyps removed, were selected randomly from a pool of 223. Dietary assessment was done through dietary questionnaire and a quantative diet history, relying upon subject recall for prior 20 years.	Those with adenomatous polyps were found to have a lower fiber/vegetable intake (p=0.04). Increased consumption of milk, beef, and beer were all significant risk factors in males.	Study combines fiber and vegetable consumption. Confounders were not considered in the model. Such as smoking, urban v. rural, exercise, total energy intake, micronutrients other than Vitamin C. Colorectal polyps are used as a proxy for colorectal cancer.
Clausen et al., 1991 (Ref 65).	Correlational	16 healthy control subjects with no history of GI disease, 17 patients with resected colonic adenomas, 17 patients with resected colonic cancer.	Freshly passed feces was homogenized with isotonic NaKCl for study in an anaerobic fecal incubation system. No patient showed signs of recurrence at the time of fecal sampling, which was at least 3 months after surgery. Patients were excluded from the group with former adenomas if they had previously had abdominal surgery, and from the group with former colonic cancer if the cancer operation had resulted in colostomy. Furthermore, intake if antibiotics within the previous two weeks caused exclusion. Both normal subjects and patients were on a ordinary Danish diet. Fecal short chain fatty acids were measured in both freshly passed feces and following incubations in vitro for 6 to 24 hours. In vitro incubations included trials with added carbohydrate substrates.	Without in vitro incubation, the total concentration and ratios of short chain fatty acids and the concentrations of individual acids including butyrate in fecal suspensions form 16 normal subjects, 17 patients with resected colonic adenomas, and 17 patients with resected colonic cancer were not significantly different. The ratio of butyrate production to total short chain fatty acid production from fiber sources added to the in vitro fecal inoculum was significantly reduced in patients with colonic cancer and adenomas compared with healthy controls after 6 hours incubation (p<.05) and more significantly reduced when the incubation times was extended to 24 hours (p<.01). The authors feel that subjects characterized by a colonic flora with a relatively low butyrate formation may have an increased risk of developing colonic adenomas and cancer	Subjects are somewhat matched by age and sex, but not completely. Polyp and cancer patients were characterized by relatively less butyrate production from fiber substrates in vitro than healthy controls. In vivo, without incubations fecal short chain fatty acid concentrations were similar in both controls and cases. It cannot be assessed whether in vivo consumption of the fiber substrates would result in findings similar to those reported in vitro.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Gregoire et al, 1991 (Ref. 64)	Clinical Trial.	43 healthy volunteers, ages and sex distribution not reported.	Volunteers were randomly allocated, after stratification by age and sex to one of 4 dietary groups: A. low fat, low fiber B. low fat, high fiber C. high fat, low fiber D. high fat, high fiber The source of fat is butter, mayonnaise, dressing, cream Bernaise sauce, and ground beef. The source of fiber is Fibread (9.3 g wheat fiber per slice) Three day food records kept by subjects just prior to intervention period. Cell proliferation was assessed with tritiated thymidine labeling of 3 rectal biopsies. Fecal pH and fecal bile acid concentrations were measured as well.	A short-term increase in dietary fat and decrease in dietary fiber does not result in a large increase in cell proliferation rate. Changes in fecal pH and fecal bile acid concentrations were not significantly different.	During the intervention, dietary variables other than the added fat and fiber were not controlled. The rate of colonic proliferation is a possible intermediary towards colon cancer, not the end point.
Soltero et al., 1990 (Ref. 56)	Case control study in Puerto Rico.	200 patients treated for right-sided colon adenocarcinoma. Neighborhood controls matched for age and sex.	Subjects (or next of kin, if dead) were interviewed with a quantative food frequency questionnaire regarding the diet 1 year prior to diagnosis. Fiber was calculated from USDA Handbook #8 (crude fiber).	Cholecystectomy was a risk factor for right sided colon cancer. Meat and poultry intake were significantly greater in cancer cases than controls. Fiber and vegetable intakes were significantly greater in controls than in cancer cases. No significant association with fat intake and cancer.	Major focus of the study was on cholecystectomy and colon cancer. Both fiber and vegetables noted as protective, and the relative contribution of each to risk reduction cannot be determined. It is not clear if all sources of fiber were considered, or only cereal fiber (discrepancy between text and table 5)

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Giovanucci et al., 1992 (Ref. 62)	Prospective study among U.S. health professionals.	42,296 health professionals, ages 40 to 75 years, in 1986. 170 documented cases of rectal or colonic adenomatous polyps. Controls- - 7, 284 subjects who had colonoscopy 1986 to 1988.	Subjects received a food frequency dietary questionnaire by mail two years after enrollment. Analyzed for crude fiber, dietary fiber and fat. Fiber sources: vegetables, fruits, or grain.	Animal fat intake significantly associated with polyps. Red meat and dairy fat significantly associated with polyps. All sources of deity fiber associated with •risk. Also, other plant nutrients (potassium, •-carotene, vitamin C, vitamin E) all inversely associated with polyp risk. These associated nutrients did not cancel out fiber's effect when entered in multiple logistic regression.	Intake of meat and fat relatively low compared to U.S. population. This may limit applicability of fiber findings. Right sided adenomas were excluded from analysis. Inference cannot be made about the impact of fiber on right sided colonic tumors. All subjects were men.

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