DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21CFR Part 101

[Docket No. 91N-0099]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements; Dietary Fiber and Cardiovascular Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Final Rule.

Summary: 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 cardiovascular disease (CVD). However, FDA is authorizing a health claim relating diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain dietary fiber (particularly soluble fiber), to a reduced risk of coronary heart disease (CHD). 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**.

On the basis of the totality of the publicly available scientific evidence, including recently available evidence, the agency has concluded that there is significant scientific agreement among qualified experts that a claim relating diets low in saturated fat and cholesterol, and high in fruits, vegetables, and grain products that contain soluble fiber, to reduced risk of CHD is supported. The evidence is not sufficient to attribute the reduction in risk to soluble fiber or to a specific type or characteristic of soluble fiber, or to other components of these diets.

EFFECTIVE DATE: May 8, 1993.

FOR FURTHER INFORMATION CONTACT: Joyce J. Saltsman, Center for Food Safety and Applied Nutrition (HFS-165), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-205-5916

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 27, 1991 (56 FR 60582), FDA proposed to deny the use on food labeling of health claims relating diets high in dietary fiber to reduced risk of CVD. The proposed rule was issued under 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, November 27,1991). 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 sections 403(r)(3) or (r)(5)(D) of the act (21 U.S.C. 343(r)(3) or (r)(5)(D)).

Section 3(b)(1)(A) of the 1990 amendments specifically requires that the agency determine whether health claims respecting 10 nutrient/disease relationships meet the requirements of section 403(r)(3) or (r)(5)(D) of the act. The relationship between dietary fiber and CVD is one of the claims required to be evaluated. In the proposed rule published in the **Federal Register** of November 21,1991 (56 FR 60582), FDA limited its review of the science to those aspects of the dietary fiber/CVD relationship for which the strongest scientific evidence and agreement already existed: dietary soluble fiber and CHD.

In the proposed rule, FDA requested written comments on its tentative determination not to authorize a health claim for dietary fiber and CVD. FDA also requested comments on the following issues: (1) Should the agency permit a claim on the label or in labeling of foods that states that diets high in fruit, vegetables, and whole grains are associated with a reduced risk of certain forms of cancer and CVD?; (2) If such statements should be permitted, what criteria should be used to identify foods that are eligible for such statements?; (3) What measures should the agency adopt to assure that consumers are not misled as to the benefit of consuming a specific product?: and (4) Does FDA have the authority to allow and should it allow health claims for foods as well as nutrients?

On January 30 and 31,1992, FDA held public hearings on all aspects of the proposed rules published in response to the 1990 amendments, including health claims for dietary fiber and CVD. In addition, because of new evidence identified from literature searches and new data submitted with comments to the proposed rule, FDA reopened the comment period on dietary fiber and CVD for 30 days (57 FR 32751, July 23, 1992).

In response to its proposed rule on dietary fiber and CVD, the agency received approximately 130 comments from consumers, consumer advocacy groups, State health departments, organizations of health professionals, the food industry, and Government agencies. A number of comments were received that were more appropriately answered in other dockets, and these were forwarded to the appropriate docket for response.

Most of the comments specific to the proposal for a health claim for fiber and CVD provided explanations in support of or in opposition to provisions of the proposed regulation. Some of the comments contained relevant scientific studies not included in the agency's proposed rule. These additional studies and those identified through literature searches that had not been previously reviewed in the proposal (56 FK 60582) are included in the agency's review below. The agency has summarized and responded to issues raised in the comments in section III. of this document.

II. Updated Review of Scientific Evidence

FDA, to ensure that it had not overlooked new and significant scientific data, reviewed human studies published since the publication of the proposed rule that it had identified in a standard literature search. In addition, FDA carefully reviewed all relevant scientific data submitted as comments. The availability of the new data was announced in a notice of reopening of comment period (57 FR 32751).

A. Human Studies

Detailed summaries of studies discussed below are presented in Table 1. FDA's explanation for separately evaluating studies on mildly to moderately hypercholesterolemic individuals and normocholesterolemic individuals is found in its proposed rule (56 FR 60587). Multiple sources of soluble fiber, including oat bran and other cereal brans, legumes, pectin, psyIlium, and guar gum, were used in these studies.

1. Hypercholesterolemics: "typical" or "usual" diets

Leadbetter et al. (Ref. 83) evaluated the hypocholesterolemic effects of increasing intakes of B-glucan, the major type of dietary soluble fiber in oat bran. A four-by-four Latin square design was used in this randomized intervention study with 40 hypercholesterolemic (total serum cholesterol 250 to 348 milligram/deciliter (mg/dL)) men and women, ages 25 to 64, in New Zealand Subjects added 0, 30, 60, and 90 grams day (g/day) oat bran to their usual diet for 1-month intervals. There was no wash-out between periods. Oat bran was provided in weighed packages and detailed advice and recipes were provided on how to incorporate it into the diet. The total dietary fiber content of the regular diets, without oat bran, ranged from 23 to 27 g/day. Results showed no significant effect of oat bran on serum cholesterol at any dose. There was no dose-related trend and no correlation between bran dose and changes in serum cholesterol. The authors stated that the oat bran used in this study was lower in soluble fiber (3.7 to 4.2 percent B-glucan) than oat bran used in studies showing a significant lowering of serum cholesterol with oat bran supplementation.

Cara et al (Ref. 84) evaluated the hypocholesterolemic properties of wheat germ in 10 hypercholesterolemic men and women (serum cholesterol 254 to 367 mg/dL), ages 35 to 68 years. Subjects consumed their regular diets for 1 week, then added 30 g/day wheat germ (2.9 g dietary fiber) for 4 weeks. At the end of the treatment period, subjects were monitored for an additional 4 weeks with no supplementation. Their base diet included 13.6 g/day dietary fiber and 6 g/day alcohol. Serum cholesterol decreased significantly (8.6 percent) after wheat germ intervention and returned to baseline during the 1 month followup period. Dietary soluble fiber and total saturated fat before and during the treatment period were not reported. The authors speculate that the high vegetable protein content of wheat germ could account for the observed results.

Karlander et al. (Ref. 85) evaluated the hvpocholesterolemic properties of beet fiber in 13 hypercholesterolemic noninsulin-dependent diabetics mellitus (NIDDM) men and women. (mean serum cholesterol of 275 mg/dL). Five subjects were on chronic beta blockers and diuretics and eight were on diet treatment with sulfonylurea (SU). This was a controlled, randomized intervention trial with cross-over design. The study was divided into three 6-week periods with a run-in period followed by either fiber intervention (20 g/day beet fiber) or the subject's regular diet for 6 weeks, then cross-over to the other diet. Obese subjects were given dietary advice to aid in weight control. Results showed no significant difference in total serum cholesterol between control and fiber periods for subjects advised to reduce energy intake. The SU group allowed significantly decreased (10 percent) serum cholesterol during the fiber phase (total cholesterol decreased from 275 to 247 mg/dL). The SU group had a slight but. significant loss of body mass during the run-in period only. There was no effect on serum triglycerides.

Spiller et al. (Ref. 87) evaluated the cholesterol-lowering properties of guar gum compared to oat bran in a 3-week, intervention trial with cross-over. Thirteen men and women, mean age 62 years, with mild to moderate hypercholesterolemia (serum cholesterol 204 to 276 mg/dL), were randomized to receive either 15 g (11 g dietary fiber, of which there was 10 g soluble fiber) of guar gum per day or 77 g/day (1.1 g dietary fiber, 5 g soluble fiber) oat fiber source, divided into three servings. The fibers were provided in weighed packets with instructions to mix the fiber with water or juice and consume before each main meal. After 21 days, subjects switched to the other fiber source. There was no wash-out between test periods. Blood samples were collected on days 14 and 21 during treatment periods. Results showed a significant reduction in serum cholesterol, compared to baseline, for both groups. Guar reduced serum cholesterol 11 percent and oat fiber 6 percent. Maximum cholesterol reduction was experienced after 14 days on the test fiber. No significant change occurred in serum cholesterol between days 14 and 21 on either test fiber, with serum cholesterol values increasing slightly but not significantly. Factors confounding these results include small sample size, the absence of a wash-out between test periods, and short treatment periods. Dietary intakes of soluble fiber were not reported.

Kawatra et al. (Ref. 68) reported significant reductions in total serum cholesterol and low density lipoprotein (LDL)-cholesterol in 20 overweight, Indonesian men and women with mild to moderate hypercholesterolemia consuming guar gum. Subjects consumed 15 g/day guar gum with their normal diet for 6 weeks. The guar was consumed 15 minutes before the main. meal in the form of biscuits (10 g guar) and mixed (5 g guar gum) with a flavored drink. Total serum cholesterol decreased 16.7 percent and LDL-cholesterol decreased 26.5 percent. Intake of total dietary fiber, dietary soluble fiber and saturated fat were not reported.

Tinker et al. (Ref. 89) evaluated the cholesterol-lowering properties of prunes in a randomized, cross-over trial. Forty-one men, ages 29 to 79, with mild to moderate hypercholesterolemia (serum cholesterol 201 to 290 mg/dL) consumed either grape juice (360 milliliter (mL)/day) or 12 prunes (100 g/day) for 4, weeks followed by cross-over to other diet for an additional 4 weeks. Prunes provided 6 to 7 g of total dietary fiber and 3.6 to 4.2 g of soluble fiber as pectin. Base diets included 18 g of total dietary fiber during the grape juice period and 24 g of fiber during the prune period. Four to five percent of the energy was from alcohol. There was no significant difference between serum cholesterol on the prune diet and on the grape juice diet.

A final report by Earll et al., July 1986 (Ref. 90), was submitted with one of the comments. This was an intervention study with seven free living hyperlipidemic (serum cholesterol ranged from 261 to 346 mg/dL) male and female patients. Subjects were asked to consume 24 g/day of corn fiber (containing less than 2 g soluble fiber) for 6 weeks, then 48 g/day corn fiber for an additional 6 weeks with their regular diet. The test period was followed by an 8-week wash-out period. Actual consumption of corn fiber was slightly less according to records kept by the subjects. Total cholesterol was reduced, on average from 298 to 253 mg/dL (significant), although much smaller changes were seen in two subjects, and one subject had an increase in serum cholesterol during the study period. In all but one of the subjects, serum cholesterol remained above 200 mg/dL with fiber intervention, suggesting dietary therapy was not adequate. The dietary intakes of the subjects before and during the test period were not recorded.

Whyte et al. (Ref. 104) reported significant reductions in serum cholesterol in 23 men with mild hyporcholesterolemia (total cholesterol ranged from 209 to 259 mg/dL) consuming oat bran. Subjects consumed 123 g/day oat bran or 54 g/day wheat bran cereal with their regular diets for 4 weeks followed by cross-over to the other fiber cereal. All subjects consumed wheat cereal during a 3-week baseline period prior to randomization to test groups. Total dietary fiber and fat intake were approximately the same between groups. Total serum cholesterol and LDL-cholesterol, when consuming oat bran, decreased 4 percent and 5.5 percent, respectively, compared to wheat bran. The authors note that one of their earlier studies with 12 g of oat bran showed significant decreases in serum cholesterol of 6 percent compared to 12 g of wheat bran. According to their analyses, both oat brans were similar in composition (Ref. 104). The smaller decrease in serum cholesterol reported in this study as compared to some other oat bran studies, not conducted by these authors, may be due to the difference in B-glucan content of different strains of oats. This 4-week study does not address long-term effectiveness of oat bran intervention.

Uusitupa et al. (Ref. 100), in a randomly-allocated, double-blind parallel group trial, tested the effects of guar gum on 39 individuals with NIDDM (mean serum cholesterol of groups: 253 and 237 mg/dL). The test group received 5 g of guar gum three times per day (estimated total of 10 g soluble fiber) before meals for 3 months, while the control group received 5 g of wheat flour 3 times per day before meals. After 3 months, the control group was switched to guar and both groups were followed for an additional 10 months. At the end of 3 months, the guar group showed a significant lowering of serum total cholesterol. Over the remaining 10 months, the group which began as the test group had an increase in total cholesterol, although it remained significantly lower than prior to the trial. The group which began as the control group, but switched to guar, demonstrated the lowest serum cholesterol during month 5 (208 mg/dL). This was followed by increasing serum cholesterol to a maximum at month 11 (242 mg/dL). After 12 months, serum cholesterol for this group was 233 mg/dL. Significant weight loss occurred in both the control and treatment groups to a similar degree. The dietary intakes for both groups were not reported.

Spencer and Gee (Ref. 109) evaluated the cholesterol-lowering properties of apple juice supplemented with 10 g of dietary fiber (70 percent soluble fiber, predominantly from gum arabic) versus plain apple juice. Thirty-one mildly hypercholesterolemic men (serum cholesterol between 200 and 270 mg/dL) consumed their regular diets in this 6-week cross-over, blinded trial. With both ordered groups totalled, there was a significant decrease in serum total cholesterol and LDL-cholesterol during the period of consumption of fiber-enriched juice. When order of presentation is considered, there were inconsistencies in the changes. The group which began the trial with the placebo did not show any change from baseline in serum cholesterol during the placebo phase, whereas the group which received the placebo during the second half of the trial maintained the lower cholesterol level which occurred during the fiber supplementation period. Cholesterol intake was significantly higher in the juice-only group.

Niemi et al. (Ref. 99), in a double-blind, cross-over trial, reported significant lowering of serum cholesterol in a group that received 15 g/day guar gum (estimated total of 10 g soluble fiber) as a supplement for 12 weeks when compared to the group which received cellulose, the placebo. The 16 women and 6 men chosen as subjects were all (NIDDM) between the ages of 40 and 76. Nineteen of these subjects were on medication for their diabetes. Although the patients were advised to maintain their normal diets, no dietary measurements were reported to verify this.

Kirsten et al. (Ref. 97) evaluated the hypocholesterolemic properties of guar gum in 13 men and women with type IIa and lIb hyperlipidemia (serum cholesterol concentration >251 mg/dL). The study was divided into three phases: the 30-day pretreatment phase (baseline), the 60-day treatment, and the 60-day post-treatment period. During the treatment phase, subjects consumed 4 g of guar gum, mixed with water or juice before breakfast, lunch, and dinner (12 g guar/day, estimated—8 g soluble fiber). Subjects were only instructed to avoid cholesterol-rich foods during the study period. Both total serum cholesterol and LDL-cholesterol decreased significantly compared to pretreatment levels. During the post-treatment period, serum cholesterol returned to baseline and LDL-cholesterol increased above baseline. The dietary intakes of the subjects during each phase of the study were not reported.

Cerda et al. (Ref. 105) evaluated the hypocholesterolemic effects of grapefruit pectin in a double-blind, placebo-controlled, cross-over study. Twenty-seven hypercholesterolemic men and women (mean serum cholesterol of 275 mg/dL) consumed 15 g of grapefruit pectin (27 tablets, 9 per meal) or 15 g of flour (also in tablet form) per day for 4 weeks followed by a 4-week wash-out before cross-over. During the pectin period total cholesterol decreased by almost 8 percent and LDL-cholesterol by 11 percent (both significantly lower compared to baseline). There was no change in serum cholesterol during the placebo period. The dietary intake of the subjects during each period of the study was not reported. The short test periods do not address long-term usefulness of pectin.

Haskell et al. (Ref. 106) evaluated the hypocholesterolemic properties of four isolated, purified soluble fibers in four separate trials. All subjects had serum cholesterol levels between 200 and 280 mg/dL and were randomized to 1 of the four studies. Study one was a 12-week intervention trial using a powdered soluble fiber mixture providing 17.2 g/day of soluble fiber. The powder consisted of acacia gum (9.7 g), psyllium (4.9 g), and guar gum (2.6 g). The soluble fiber mixture was tested against a fructose placebo (15 g/day). Results showed no statistically significant changes from baseline to 6 or 12 weeks within or between groups. Study two was a 4-week intervention testing 15 g/day of acacia gum powder against 15 g/day fructose powder. There was no significant change from baseline or compared to the placebo. Study three was an 8-week cross-over trial using 10 g/day of guar (estimated 6.7 g soluble fiber) as a control and a 15 g/day fiber mixture of pectin (3.9 g), psyllium (6.3 g), guar (3.3 g), and locust bean gum (1.5 g). Each test period was 4 weeks. Results showed both the guar and the fiber mixture reduced serum cholesterol (approximately 10 percent and 8 percent, respectively), LDL-cholesterol (approximately 14 percent and 12 percent, respectively), and high density lipoprotein (HDL)-cholesterol (about 6 percent) significantly. Study four was a 4-week dose-response study with increasing amounts of soluble fiber from a mixture of pectin, psyllium, guar, and locust bean gum. Three groups received either 5 g, 10 g, or 15 g/day of the mixture. Results showed that the serum cholesterol and LDL-cholesterol of the group consuming 15 g/day was significantly lower than the placebo.

A 1984 study by Anderson et al. (Ref. 110) was submitted with comments in support of a long-term hypocholesterolemic effect of soluble fiber from oat bran and beans. Ten men, ages 46 to 66, with serum cholesterol above 260 mg/dL were randomly assigned to oat bran or bean-supplemented diets for 21 days following a 7-day baseline period on a metabolic ward. The base diet was a "typical" American diet with 38 percent of calories as fat and 450 mg cholesterol. To this diet, the subjects added either 100 g of oat bran or 100 g of dried beans per day. Both of these diets provided 18 g of total soluble fiber and 48 to 50 g of total plant fiber per day. Before discharge, the subjects were instructed on the use of a high fiber (50 g of total fiber per day) maintenance diet with oat or bean product supplements at home. The high fiber diet was also low in fat (30 percent of calories as fat), low in saturated fat (10 percent of calories), and low in cholesterol (150 mg/day). Ten men were followed on their home diets for 24 weeks and 4 for 99 weeks. Results of the metabolic ward phase of the study showed that the oat bran and bean diets lowered serum cholesterol significantly (23 percent) over the 3-week period compared to baseline. At 24 weeks (the followup phase), serum cholesterol levels were significantly (26 percent) lower than baseline. Cholesterol levels in the four men followed for 99 weeks were 23 percent lower than baseline (significant at p<0.00255). Reductions in LDL-cholesterol were also significant during both phases of the study. HDL-cholesterol decreased significantly(20 percent) during the metabolic ward phase but increased during the long-term followup. All 10 subjects lost approximately 4 pounds (Ib) (significant at p<0.0025) during the metabolic ward phase of the study. The investigators reported that changes in body weight were not significantly correlated with the changes in serum cholesterol. An additional 4 lb of weight was lost during the 24-week phase of followup.

An unpublished study (Ref. 119) evaluated the cholesterol lowering properties of oat gum in hypercholesterolemics (mean serum cholesterol of 255 mg/dL). Instant oat gum (3.6 g) or a placebo (maltodextrin) were mixed with a noncarbonated diet fruit drink (250 mL) and consumed twice a day at each main meal for 4 weeks. There was a 3-week wash-out between treatment periods and after the last oat gum period. Subjects were randomly assigned to start the treatment period with either the oat gum beverage or the placebo. Results showed significantly lower serum cholesterol after 4 weeks on oat gum compared to both the baseline (p = 0.02) and the placebo (p = 0.001). Although subjects were asked to maintain their weight, subjects' weights were not reported.

Bridges et al. (Ref. 120) evaluated the effect of oat bran on serum cholesterol and serum acetate in hypercholesterolemic men admitted to a metabolic ward. Animal studies have shown that both acetate and propionate inhibit cholesterol synthesis (Ref. 120). The 20 subjects were divided into two groups: Wheat bran group (mean serum cholesterol of 252 mg/dL) and oat bran group (mean serum cholesterol of 305 mg/dL). Following 1 week of a typical American diet, the diets were supplemented for 21 days with either 110 g of oat bran per day or 40 g of wheat bran. Results showed that the oat bran group experienced significantly lower (p = 0.05) serum cholesterol than the wheat bran group. However, in the wheat bran group, the baseline cholesterol level had been higher than in the oat bran group. There was a significant (p = 0.001] weight loss in both groups. The weight loss appeared to be greater in the oat bran group. LDL-cholesterol was significantly lower (p = 0.005) in the oat bran group as compared to the group's pretreatment values. There was no significant difference in LDL-cholesterol between groups. Serum acetate values were significantly higher in the oat bran group than in the pretreatment diets. Wheat bran did not change serum acetate significantly compared to the pretreatment diets.

Kashtan et al. (Ref. 121) evaluated the effects of wheat bran and oat bran supplements on blood lipids and lipoproteins in 84 subjects with mild hypercholesterolemia. This was a controlled, parallel, double-blind study in which subjects consumed either oat bran supplements (with, 11 to 17 g - dietary fiber and an estimated 5 to 8 g of soluble fiber) or a wheat bran cream of wheat mixture (11 to 17 g of dietary fiber) each day for 14 days. Defined diets were delivered to the subjects' homes. The diets provided one of four energy amounts: 1,600, 2,000, 2,400, and 2,800 calories, with 37 percent of energy as fat, 47 percent carbohydrate, and 16 percent protein. Results showed mean serum cholesterol decreased significantly (-10.8 percent, p = 0.001) in the oat group compared to the wheat group (-4.7 percent). However the baseline cholesterol was higher among the oat bran group. The wheat bran group also experienced significantly decreased serum cholesterol compared to their baseline (p <0.001). LDL-cholesterol decreased significantly compared to baseline for both groups (p = 0.03 for the wheat bran group and p <0.001 for the oat group). The short test period of 2 weeks in this study interpretation of the results difficult.

Ranhotra and coworkers (Ref. 122) studied lipidemic responses in 17 hypercholesterolemic men consuming foods high in soluble fiber. This was a 6-week intervention study with a 6-week control period prior to the test period. Subjects consumed their usual diet during the control period and kept daily records of intake for 4 weeks. Subjects were then given a list of foods that were identified as good sources of soluble fiber and a diet supplement containing 30 g each of rice bran and oat bran, and were instructed to incorporate foods on the list into their usual diet. Each subject served as his own control. Results showed that only 6 (34 percent) of the 17 Subjects were responders to the soluble fiber intervention. The authors reported that not all subjects consumed the supplement daily and that intakes of soluble fiber varied greatly among the participants. Serum cholesterol values decreased from 1 percent to 17 percent compared to individual control levels in those responding to soluble fiber. However, the authors did not perform a statistical analysis of the results, and the results in this study are too inconsistent in direction and magnitude to support an effect of soluble fiber on serum cholesterol.

Zhang et al. (Ref. 123) studied the Mechanism of cholesterol lowering in nine subjects with ileostomies. This was a randomized, controlled, cross-over study design. Subjects were instructed to consume, their own food, which was modified to be low fiber, and assigned to either a low fiber diet (supplemented with wheat-flour bread) or a high fiber diet (supplemented with oatbran bread) for 3 weeks followed by cross-over to the other fiber bread for another 3 weeks, Ileostomy effluents were collected on sampling days in both dietary periods. Subjects were also divided into two subgroups according to the amount of bile acids excreted in the ileostomy effluents. Results showed subjects with low bile acid excretion had significantly increased daily excretion of total bile acids on the high fiber diet as compared to the low fiber diet. There wore no significant differences in daily excretion of total bile acids between the high fiber period and the low fiber period in subjects with high daily bile acid excretion. There was no baseline serum cholesterol measurement. Compared to the low fiber period, serum cholesterol and LDL-cholesterol decreased significantly (p = 0.01 and p = 0.05, respectively) in all nine subjects on the high fiber diet. Subgroup analysis showed that subjects with low daily bile acid excretions had significantly reduced serum cholesterol on the high fiber diet than on the low fiber diet. Subjects with a high doily excretion of bile acids showed no significant difference in serum cholesterol between the test periods. Conclusions about fiber mechanisms in towering serum lipids in subjects with ileostomies may not apply to the general population.

2. Hypercholesterolemics: Step 1 or 2 diets

A study by Israelsson et al. (Ref. 86) was submitted with a comment. This placebo-controlled, double-blind, cross-over intervention study used 39 g/day beet fiber or bread. Twenty-seven hypercholesterolemic (serum cholesterol 263 to 297 mg/dL women, 55 to 56 years old, were chosen from a CVD screening program. Subjects consumed a moderate cholesterol, low fat diet with increased polyunsaturated fatty acids/saturated fatty acids (PUFA/SFA) for a 1-month run-in period and were then randomized to the fiber group or placebo for 1 month followed by cross-over to the other diet. The beet fiber provided 6 g soluble fiber, 16.5 g insoluble fiber, and 22.5 g total dietary fiber. Subjects decreased alcohol intakes after the run-in period. No data on saturated fat or soluble fiber intakes were provided. Results showed a significant reduction in serum cholesterol in the fiber group compared to the placebo after 2 weeks, but not after 4 weeks. LDL-cholesterol showed a modest but significant reduction after 4 weeks of fiber intervention. HDL remained constant or increased significantly after 1-month intervention. The ratio of LDL:HDL was significantly reduced at the end of the test period. The short test period of this study does not address long-term effectiveness of beet fiber.

Bremer et al. (Ref. 91) evaluated the cholesterol lowering effects of oat bran and wheat bran in a randomized, single-blind, cross-over, placebo-controlled intervention trial. The fibers were incorporated into breads. Twelve hyperlipidemic men and women (total serum cholesterol 220 to 348 mg/dL) were stabilized on a American Heart Association (AHA) phase II diet (total fat 25 to 30 percent of energy, saturated fat <8 percent of energy, polyunsaturated fat 5 to 10 percent of energy, cholesterol <250 mg/day) for 3 months prior to intervention. There was a 2 week run-in prior to test during which subjects added additional bread to their diets. Subjects were randomized to one of the two fiber groups for 4 weeks, followed by 2-week wash-out, then cross-over to other fiber group. The bread (10 to 12 slices/day) was added to the diet in place of other carbohydrate foods. Subjects had a mean intake of 44.6 g/day of oat bran (range of 34.2 to 68.4 g/day). Total dietary fiber intake during the oat period was 32.2 g, and 34.1 g during the wheat period. Results showed no significant differences in total serum cholesterol or LDL-cholesterol ‘between the oat and wheat periods. Authors account for the lack of observed response on serum cholesterol from oat bran as due to the lower soluble fiber content of New Zealand oat bran compared to oat bran used in other studies.

Anderson et al. (Ref. 92) evaluated the hypocholesterolemic effects of two bulk laxatives, relative to psyllium and a placebo (cellulose), in mild to moderately high hypercholesterolemic (total serum cholesterol 200 to 300 mg/dL) men and women. The laxatives were evaluated at the manufacturer's recommended dosages. Of the 163 subjects screened, 105 completed the 16-week study. Subjects were instructed in and consumed the AHA Step 1 diet (total fat 30 to 33 percent of energy, saturated fat 10 percent of energy, carbohydrate 46 percent of energy, cholesterol <300 mg/day) for 8 weeks followed by an 8-week parallel treatment with diets supplemented with one of three fiber supplements or placebo. Fiber sources used were the following bulk laxatives: psyllium (10.2 g/day), methylcellulose (6 or 10.2 g/day), calcium polycarbophil (4 g/day), and cellulose placebo (4 g/day). The authors note that psyllium and methylcellulose were most effective in lowering serum cholesterol. There was no significant difference between psyllium and methylcellulose in lowering serum cholesterol. Soluble fiber was not controlled in this study. Subjects on psyllium had the highest soluble fiber intake. Side effects were reported for each laxative.

An unpublished manuscript entitled “High soluble fiber foods reduce serum lipids even when diets are already low in saturated fat and cholesterol” (Ref. 93) was received as part of a comment. This 4-week, cross-over, metabolic study in 12 hyperlipidemic (mean total cholesterol of 272 mg/dL) subjects compared a psyllium cereal/low fat diet (9.35 g psyllium/day = ≤ 3 oz of psyllium cereal) with a similar diet substituting wheat bran for the psyllium cereal. The low fat diets were the same in both phases of the study, low in saturated fat (<4 percent of energy) and cholesterol (<50 mg/day) and high in carbohydrate (>60 percent of energy). The psyllium cereal was significantly more effective in lowering total and LDL-cholesterol than the wheat bran cereal. Mean total cholesterol reduction was from 272 mg/dL to 249 mg/dL, and from 192 mg/dL 172 mg/dL for LDL cholesterol. Preliminary subgroup analysis by the authors of the study suggested that patients with both elevated cholesterol and triglycerides (Type lIb) showed no reduction in LDL cholesterol, while patients with only Type IIa (isolated elevation of cholesterol) benefited. Additional concerns are raised by this study regarding the usefulness of psyllium in Type lIb patients.

An unpublished manuscript entitled “High fiber foods reduce serum lipids even on diets low in saturated fat and cholesterol” (Ref. 94) was received as a comment. This was a cross-over study with 11 hyperlipidemic volunteers. Each 16-week test period was separated by a 2-month wash-out period during which subjects consumed only the Step 2 diet (total fat <20 of energy, saturated fat <7 percent of energy, cholesterol <100 mg/day, and carbohydrate >60 percent of energy). During one metabolic phase, subjects were fed foods considered good sources of soluble fiber (e.g., legumes and psyllium-containing cereals) as part of the Step 2 diet. During the second phase, wheat bran-containing foods were fed. Results showed that both the soluble- and insoluble-fiber groups lost weight during the 4-month test period. The insoluble-fiber group lost significantly more than the soluble-fiber group. Although, blood lipids fell on both diets, total cholesterol, LDL- and HDL-cholesterol values were significantly lower (6.3 percent, 8.6 percent, and 5.7 percent, respectively) in the soluble-fiber group than in the insoluble-fiber group. The soluble fiber diet emphasized foods shown in other studies to reduce serum cholesterol, i.e., dried beans, peas, other legumes, oat bran, and a psyllium-containing cereal. The actual difference in soluble fiber content between the soluble and insoluble fiber diets was only about 3.2 g/day, on average. The authors felt that the specific foods they fed contribute to lowering of serum cholesterol, but expressed concern that not all soluble fibers show this effect, and that no mechanism of action is apparent. They, therefore, expressed “concern over lipid lowering claims for direct dietary fibers.”

An intervention study by Anderson et al. (Ref. 95) with 44 hyperlipidemic (serum cholesterol 200 to 300 mg/dL) men and women was conducted using a randomized, double-blind, and parallel design. Subjects consumed a Step 1 diet and 3.7 ounce (oz)/day (on average) of either a wheat bran cereal or a psyllium cereal for 6 weeks. The psyllium cereal provided 10.7 g/day of psyllium. The psyllium group had a lower total cholesterol by about 8 percent and LDL cholesterol by nearly 13 percent by the end of the study. Mean total cholesterol, however, was still higher than 200 mg/dL despite these reductions. Both groups had comparable weight loss of about 1 (lb) pound. Because this study had a short test period, it did not address the long-term usefulness of psyllium in reducing serum cholesterol. In a parallel design, nonblinded clinical trial with 59 men and women with total cholesterol between 215 and 396 mg/dL, Neal and Balm (Ref. 98) placed all subjects on Step 1 diets for 7 weeks. The control group continued on the Step 1 diet, and the test group received 20.4 g of psyllium per day in the form of Metamucil immediately after breakfast and the evening meal for 13 weeks. After the treatment period, the psyllium group had a decrease in total cholesterol of 7.1 percent, while the control group had a 1.6 percent decrease. The difference between the test and control groups was 5.5 percent, a significant decrease. Although there was a 5.1 percent decrease in LDL in the psyllium group compared to the control, this decrease was not significant. The authors failed to report the amounts of total fat, saturated fat, and total soluble dietary fiber consumed during each period.

Two short-term studies by Wolever et al. (Refs. 101 and 102) evaluated the effectiveness of psyllium in lowering serum cholesterol (Ref. 101) and its effectiveness when psyllium was taken with meals or between meals (Ref. 102). These studies were done with men and women, some of whom were on lipid-lowering drugs, who were instructed on a Step 2 diet. The test periods were for 2 weeks. In both studies, serum cholesterol was lowered significantly at the end of the 2 weeks.

O'Conner et al. (Ref. 103) conducted a well-controlled multicenter, double-blind randomized, parallel group, placebo-controlled trial with men and women between the ages of 18 and 70 years with a diagnosis of mild to moderate primary hypercholesterolemia (see Table 1). A five fiber supplement, containing guar and pectin and providing 7.5 g of soluble fiber and 2.5 g of insoluble fiber, was administered either once or twice a day for 15 weeks with a Step 1 diet. The placebo group received 5.2 g of insoluble fiber with no soluble fiber before breakfast and dinner. All nutrients were kept constant except for fiber. Serum cholesterol and LDL-cholesterol were significantly reduced compared, to placebo in all studies (see Table 1, studies B301 and B302 in). An extension of this study evaluated the long-term usefulness of the five fiber supplement for an additional 36 weeks (total of 51 weeks). Significantly reduced levels of total, and LDL-cholesterol were maintained (5.3 percent and 8.4 percent, respectively) compared to baseline. This study shows both the ability of a particular soluble fiber product for reducing blood lipids and the long-term benefits of soluble fiber supplementation with a low fat diet.

An unpublished study (Ref. 108) evaluated the hypocholesterolemic effect of psylliurn in 23 hypercholesterolemic men (mean total cholesterol greater than 24.0 mg/dL). Using a double-blind, double cross-over design, the subjects were randomly assigned to either the psyllium-wheat bran-psyllium, group or to the wheat bran-psyllium-wheat bran group for 8, 5, and 5 weeks, respectively. Subjects consumed a total of 10 g of soluble fiber/day from psyllium and 2 g of soluble fiber per day from wheat bran. All subjects consumed a Step 1 low fat diet as the base diet. Results showed significant .cholesterol and LDL-cholesterol lowering (4.3 percent) with psyllium compared to the wheat phase of the test. Initial cholesterol values for each group were not given.

A 1987 study by Turnbull and Leeds (Ref. 111) was submitted with comments from the food industry as further evidence for a hypodholesterolemic effect of soluble fiber from oat bran. In this study, 17 living men and women aged 23 to 73 years (serum cholesterol levels above 232 mg/dL) were given varying degrees of instruction on a low fat diet (<35 percent calories from fat). All subjects followed this diet for a 1-month run-in period. Eight subjects were followed intensively during the run-in period, and fiber periods through blood sampling and diet histories. Subjects were then randomly assigned to receive either 150 g/day oats (from cereal and muffins) or 100 g/day wheat flour biscuits for 1 month followed by cross-over to the other fiber diet for an additional month. The oat products provided 5.4 g of soluble fiber per day. The wheat products provided 3.1 g/day. Results during the run-in period showed a significant loss of weight and reduction in serum cholesterol in the group of eight subjects studied intensively during the first: month. At the start of the first test period (whether oat or wheat) all subjects had a mean fat intake of 34 percent of calories. During the oat period, the subjects' energy intakes increased and fat intake increased to 35 percent. Mean body weight, however, remained constant. Combining all results from the oat-wheat and wheat-oat periods, serum- and LDL-cholesterol fell significantly (p = .02 and p = 0.003, respectively). During the wheat period, the subjects' caloric intake increased with a mean body weight increase of 0.3 kilogram (kg). Total fat consumption during the wheat period was 36 percent of calories. Mean serum cholesterol of the combined period showed a nonsignificant, increase (1.6 percent) in serum cholesterol, during the wheat period. LDL-cholesterol showed a nonsignificant increase. In the eight subjects followed intensively throughout the study, the results showed that most of them had further reductions in total and LDL-cholesterol on the oat diet beyond the low fat diet alone. In a later study (Ref. 126) of the same design and using the same levels of oats and wheat flour, the authors reported favorable changes in apolipoprotein A1 and no change in apolipoprotein B in subjects on the oat diet.

The purpose of the study by Fukagawa et al. (Ref. 114) was to evaluate the effects of a very high carbohydrate high fiber (HCF) diet on peripheral-tissue insulin responsiveness in a group of healthy young men (ages 18 to 24 years, Group A) and in a group of older men and women (ages 67 to 86 years, Group B). The young men had normal serum cholesterol (199 mg/dL) and the older adults were hypercholesterolemic (237 mg/dL). The subjects were studied while consuming their usual ad libitum diet and after consuming a HCF diet for 21 to 28 days. The older group was admitted to the metabolic ward for the duration of the study. The younger subjects only ate their meals on the metabolic ward. The study was not blinded or placebo controlled. Test diets provided the following: Group A—-23.6 g/day soluble fiber, 88.2 g of plant fiber/day, 134 mg dietary cholesterol, 14 percent energy as fat, 3 percent energy as saturated fat, 69 percent of energy as carbohydrates; Group B— 17 g of soluble fiber, 67.7 g of plant fiber/day, 90 g of dietary cholesterol, 15 percent energy as fat, 3 percent energy as saturated fat, and 70 percent energy as carbohydrates. Results showed a significant reduction in serum cholesterol in both groups after 4 weeks (Group A: 26 percent; Group B: 45 percent). The results of this study are inconclusive for an effect of fiber on serum cholesterol (which was not the objective of the study) because the subjects' ad libitum diets were significantly higher than the test diet in fat (37 to 42 percent of calories compared to approximately 14 percent on the test diet), saturated fat (15 to 17 percent of calories versus 3 percent of calories), and lower in carbohydrates (40 to 45 percent of calories versus 68 to 70 percent of calories). In addition, there was no control group.

Anderson et al. (Ref. 118) evaluated the cholesterol-lowering benefits of psyllium-enriched cereal in subjects with mild to moderate hypercholesterolemia (serum cholesterol range of 200 to 300 mg/dL. Subjects consumed their usual diets for 1 week before being randomly assigned to receive psyllium-flake or wheat bran flake cereal for 6 weeks. Subjects were also instructed on a Step 1 diet and asked to adhere to it for 6 weeks. Soluble fiber intake during the treatment period was 5.9 g per day for the wheat bran group and 15.1 g/day for the psyllium group. Results showed significantly reduced serum- and LDL-cholesterol in the psyllium group compared to the wheat group. Serum cholesterol was reduced 8.36 percent ($p = 0.01$) and LDL-cholesterol 12.9 percent ($p = 0.01$) in the psyllium group. There was no significant change in serum- or LDL-cholesterol in the wheat group.

3. Normocholesterolemics: "typical" or "usual" diets

Resnicow et al. 1991 (Ref. 96), measured total serum lipids in a population of 31 Seventh Day Adventists, ages 5 to 46 years, who had consumed a pure vegetarian diet for at least 6 months prior to taking of blood samples. Diets of vegans were compared to those of omnivore controls. Blood samples were not taken from the controls and blood values for these subjects were derived from the Lipid Research Clinics Population Studies Data Book. Results showed that the adult vegans consumed significantly less energy and energy from fat (31 percent versus 38 percent of calories), total fat, saturated1 fat, monounsaturated fat, cholesterol, and protein. They also consumed significantly more fiber (45 g/day versus 20 g/day) than the omnivores. Total dietary soluble and insoluble fibers were not assessed. Foods consumed in greater frequency by vegans included almonds, cashews, and their nut butters, dried fruits, citrus fruits, soy milk, and greens. Total serum cholesterol for vegans was approximately 23 percent lower (139 mg/dL versus 182 mg/dL) than expected values for omnivores.

One study submitted with comments evaluated the effect of glucomannan, a pectin-like gel fiber derived from purified tubers of *Amorphophallus koniac* K. Koch, on serum cholesterol and weight reduction in obese patients consuming their normal diets (Ref. 117). Weight loss and serum cholesterol decreased significantly in the test group compared with the placebo group at the end of the 8-week trial. After 4 weeks on the test product, subjects had a mean weight loss of 4.9 Ib and mean serum cholesterol reduction of 20.9 mg/dL. After another 4 weeks, weight loss was only 0.6 Ib and serum cholesterol was reduced only 0.8 mg/dL. Because weight loss and serum cholesterol are closely correlated, the effect of glucomannan on serum cholesterol cannot be determined from this study.

An unpublished study studied the mechanism of serum cholesterol reduction by oat bran (Ref. 124). This was a 2-month metabolically-controlled intervention trial with nine normocholesterolemic men. A single isotope was used to determine bile acid kinetics during the oat bran period. During the first month, subjects consumed a constant diet provided in a metabolic unit. The fat content of the diet was 35 percent of the energy. The total soluble fiber content of the low fiber diet ranged from 3.0 to 4.9 g/day and for the high fiber period 9 to 12 g/day. During the second month, this same diet was supplemented with 100 g of oat bran per day. Results showed significantly lowered serum cholesterol during both periods. Serum cholesterol was 14 percent lower compared to the prestudy period during the low fiber period and 22 percent lower during the high fiber period. Serum cholesterol during the high fiber period was also significantly lower than that of the low fiber period (an additional decrease of 9 percent). Bile acid excretion approximately doubled during the high fiber period.

4. Normocholesterolemics: low fat diets

Nervi et al. (Ref. 107) reported that an intake of 120 g/day of legumes for 30 to 35 days significantly lowered serum cholesterol (from 162 to 143 mg/dL) in 20 Chilean young men compared to responses of men on a control diet. The men consumed beans, peas, or lentils each day as part of a diet that provided 33 percent of calories from fat and 12.5 g of total fiber. The study was designed to evaluate the hypothesis that legumes may be a risk factor for cholesterol gallstones in certain subpopulations. The authors reported significantly increased biliary cholesterol saturation and modification of bile acid composition during the legume diet period.

5. Other studies

Evidence for the cholesterol-lowering effect of soluble fiber from oats was evaluated using meta-analysis (Ref. 125). In this study, after pooling the raw data from 5 investigators who had looked at the effect of consumption of oat products on blood total cholesterol, a modest reduction (average decrease of 5 to 6 mg/dL) on blood total cholesterol levels was found. The decrease in blood total cholesterol was largest in those trials with initially higher blood total cholesterol levels, particularly where an intervention dose of 3 g or more of soluble fiber from oats was used. To assess whether other dietary factors, i.e., dilution of saturated fat and calorie intakes by the oatmeal or oat bran addition to diets, might have been responsible for the drop in blood total cholesterol levels, the authors used the experimentally derived, predictive equation of Keys to see if dietary changes in fat components of the test diets could account for the observed decreases in serum cholesterol. The fat and saturated fat changes did not appear to be responsible for the drop in serum cholesterol levels, thus suggesting that some other factor in the test diets (e.g., the soluble fiber fraction) was responsible for the observed effects. The authors concluded, therefore, that incorporation of oats (a rich source of soluble fiber, primarily as β-glucan) into diets causes a modest decrease in average blood cholesterol. The authors also suggested that there was a close-response relationship between the amount of soluble fiber from oats and the reduction in blood cholesterol levels, with intakes of soluble fiber from oats above 3 g/day showing more effect than lower intakes. Additionally, the authors noted that other components in oats may play a role in the observed cholesterol reduction and suggested the need for long-term clinical trials (6 months or more) with multiple doses to verify their conclusions from the meta-analysis.

6. Summary of human studies

The human studies reviewed above suffered from many of the same design flaws noted in the proposed rule on health claims for dietary fiber and cardiovascular disease (56 FR 60582 at 60591). Some studies were conducted with very smell sample sizes (Refs. 84, 85,67, 90, 91, 93, 94, 97,110, 111, 114, 122, 123, 124, and 126). Another limitation was short study times (Refs. 87,101,102,110,114,120,121,and 123). Inadequate control of confounding factors, such as concomitant weight losses and changes in other dietary components which may have affected results, plagued some studies (Refs. 86, 96,107,108,110,117,119, and 120). The absence of adequate dietary intake data to assure that dietary changes other than differences in soluble fiber intakes had not occurred was a problem for a number of studies (Refs. 84, 86, 87, 88, 90, 91, 85, 97, 99,105, 106, 119, and 123).

Several studies were suggestive of positive effects of soluble fiber intakes on blood cholesterol levels. One study provided evidence of a relationship between consumption of foods high in soluble fiber and reduced levels of blood total- and LDL-cholesterol levels (Ref. 118). In a comparison of a breakfast cereal fortified with psyllium, a rich source of soluble fiber (12 g of psyllium/day from 114 g/day of a psyllium containing cereal) to a wheat bran cereal which contributed negligible amounts of soluble fiber, the psyllium-containing cereal was associated with lower blood total- and LDL-cholesterol levels after 6 weeks than were observed in subjects following a diet containing wheat bran cereal. In another study (Ref. 104), consumption of 123 g of oat bran cereal (contributing 10.3 g soluble fiber daily) versus consumption of 54 g of wheat bran cereal per day (contributing 3.4 g of soluble fiber daily) was associated with lower blood total- and LDL-cholesterol levels after 4 weeks. Dietary intakes of fat and saturated fat were estimated to be similar across treatments. On the other hand, some studies found no relationship between intakes of high soluble fiber diets and blood total- or LDL-cholesterol levels (Refs. 83 and 91).Several explanations for the lack of a relationship in these studies were offered by the authors, including the possibility that the oat bran used was low in soluble fiber content (Refs. 83 and 91). The study by Neal and Balm (Ref. 98) showed significantly lower blood total-cholesterol levels with consumption of a psyllium fortified cereal, but the decline in LDL-cholesterol levels compared to the control was not statistically significant. A small body weight loss in both groups may have confounded the relationships. However, since it is the LDL-cholesterol rather than the total-cholesterol, that is the desired endpoint for evaluating beneficial changes, the lack of statistical significance for serum LDL-cholesterol levels limits this study's usefulness.

Finally, the meta-analysis on the cholesterol-lowering effect of oat products was useful and suggested a benefit from oat consumption. However, the authors noted that, while grams of soluble fiber were chosen to represent the dose of oat product, it is entirely possible that other components of oats, as well as the way in which the oat product is prepared, may also play a role in reduction of blood LDL-cholesterol levels. The authors recommended that, because there are several components of oats which could provide beneficial effects on blood cholesterol levels, future clinical studies should test multiple doses of oat products with the simultaneous measurement of other possible active components, including soluble fiber, β-glucan, and tocotrienols.

The most definitive results linking soluble fiber intakes to beneficial changes in blood cholesterol levels were for studies in which dietary supplements of guar (Refs. 99 and 100), gum arabic (Ref. 109), psyllium (Ref. 92), or a combination of soluble fiber sources (Ref. 103) were given. Some of these studies (Refs. 99, 100, and 109) also, however, failed to provide adequate information on dietary intakes, thus limiting the ability to rule out possible confounding effects from other dietary changes that may have occurred concomitantly with addition of these supplements. A series of well-conducted clinical trials were done to design and test the effectiveness of fiber mixtures (guar, pectin, psyllium, and locust bean) on blood cholesterol levels (Refs. 103 and 106). Early studies in one series (Ref. 106) showed no benefit from acacia gum alone or a mixture of acacia gum, psyllium and guar (Studies 1 and 2). Only when a mixture of pectin, psyllium, guar and locust bean was given were beneficial effects seen (Study 4). These results strongly suggest that benefits of fiber supplements are not readily predicted by an analytical definition of soluble fiber, but rather vary, in some unknown way, among different sources or combinations of sources, of soluble fiber. Thus, generalizing results from one fiber source to another must be done cautiously.

B. Animal studies submitted with comments

FDA received a number of animal studies submitted as comments. FDA has reviewed these studies as described below.

1. Relationship between specific soluble fibers and plasma cholesterol.

Ney et al. (Ref. 127) evaluated the effect of soluble oat fiber on blood very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) levels by feeding male rats cholesterol-raising diets (diets which contained 1 percent cholesterol and 0.2 percent cholic acid as the stimulus for increasing blood cholesterol levels) and 6 percent dietary fiber from cellulose (control) or from three oat products with increasing levels of soluble fiber: Oat bran, high fiber oat flour or a processed, oat product. Compared to the cholesterol-fed cellulose controls all oat fibers lowered plasma total cholesterol by 25 to 45 percent, lowered VLDL + LDL cholesterol levels by 40 to 60 percent, and raised HDL-cholesterol by 25 to 40 percent (all significant at p = 0.01). This pattern of changes in blood lipid components is associated with decreased risk of heart disease. The processed oat product, which contained 40 percent more soluble fiber than oat bran or oat flour, resulted in a lipoprotein profile similar to that obtained without the cholesterol-raising stimulus of dietary cholesterol and cholic acid. The oat product with the highest soluble fiber content was, therefore, more effective with ingestion of the cholesterol-raising diet than was the oat bran or oat flour with lower amounts of soluble fiber. The authors suggested that these data, which show greater benefits as the soluble fiber content increases, support the suggestion that soluble fiber is the component of oat fiber responsible for the cholesterol-lowering effect of oat-containing diets.

Nishini et al. (Ref. 128) evaluated the effect of dietary fibers from oat bran, wheat bran, cellulose, and pectin on plasma lipoproteins, apolipoproteins, and enzymes involved on cholesterol metabolism in non-fasted rats. The animals were fed experimental diets estimated to contain 8 percent dietary fiber by weight. Results showed that pectin-fed animals (i.e., animals receiving the highest soluble fiber) had significantly lower serum cholesterol, HDL-cholesterol, and apolipoprotein A-1 levels compared to the fiber-free control. Total cholesterol levels in the wheat-bran-fed (primarily insoluble fiber) or oat bran-fed (mixed soluble/insoluble fiber) animals were not significantly different from the fiber-free control. No data were given on the soluble fiber content of the diets, although the pectin diet would be expected to have the highest level of soluble fiber. Results showed that blood lipid distributions are affected differently by dietary fibers, and that changes among lipid components frequently occurred without a change in overall cholesterol concentrations.

Prentice et al. (Ref. 129) compared the effects of ground and rolled caryopses of barley and rolled oats to ground corn on hepatic cholesterol and fatty add synthesis in chickens. Approximately 7 to 8 percent of the barley and oat cereals was β-glucan; corn had less than 1 percent β-glucan. Both barley and oats decreased plasma total cholesterol by 32 percent and 25 percent, respectively. The authors attributed the effect on serum cholesterol to the higher soluble fiber content of barley and oat diets.

Summaries of unpublished animal studies (Ref. 130) suggested that oats may be effective in lowering plasma cholesterol compared to controls fed white flour, wheat flours or corn starch. However, the data were preliminary and, thus, had limited usefulness.

Other summaries of unpublished animal studies (Ref. 136) suggested that rolled oats (75 percent by weight in diet) significantly lowered serum cholesterol in chicks. Extruded oat bran, equivalent to 47 percent of oat bran by weight in the diet, significantly-depressed (p = 0.05) serum cholesterol in chicks. Oat gum at 0.05 percent and 0.10 percent by weight in the diets of rats significantly lowered serum cholesterol. Data comparing several oat fractions fed to chicks suggested that oat gum may be the active cholesterol depressant component, and that ground rolled oats and instant oatmeal are equal in effect to the defatted, defibered oat flour. The oat oil also had a depressive effect. Additionally, pectin (high soluble fiber) was found to significantly lower serum cholesterol in rats. These studies were done in the mid-1970's and did not have analyzed values for soluble fiber content of the respective diets. Methods and data were not well described, making results difficult to interpret.

Qureshi et el. (Ref. 131) reported the effects of diets supplemented with either corn (61.5 percent by weight of the base diet), wheat (75 percent of the diet), barley (73.5 percent), oats (74.5 percent), or rye (73.5 percent) on serum cholesterol in chickens. This was pert of a study to investigate the effects of dietary cereals on the metabolic regulation of lipid metabolism in chicken livers. Compared to corn, barley and oats lowered serum cholesterol 45 percent and 32 percent, respectively. Presumably, barley and oats were higher in soluble fiber content than was corn. However, no fiber content data were presented. Additionally, body weights for animals consuming the barley and oats diets varied, making it difficult to ascribe the effects to fiber per se.

Ranhotra and co-workers (Ref. 132) evaluated the effect of oat bran and oat bran concentrate on serum lipids in rats. Animals were fed experimental diets containing oat bran (5.57 percent soluble fiber) or oat bran concentrate (13.75 percent soluble fiber). Results showed the high soluble fiber content of the oat bran concentrate was associated with a significantly lower cholesterol level, but that the oat bran diet (which contained lower amounts of soluble fiber) and the diet free of soluble fiber were not associated with lower serum cholesterol levels.

Shinnick et al. (Ref. 133) evaluated the ability of various sources and forms of oat fiber to lower plasma and liver cholesterol in male rats fed a diet with 6 percent dietary fiber as cellulose (0 percent soluble fiber), oat bran (7 percent soluble fiber), high fiber oat flour (8 to 10 percent soluble fiber), or one of four processed high fiber oat flours (8 to 12 percent soluble fiber). All diets were supplemented with 1 percent cholesterol and 0.2 percent cholic acid to stimulate increased levels of blood total cholesterol. Results showed that all oat products significantly lowered serum cholesterol compared to the control. In a second experiment, diets containing 4 percent dietary soluble fiber in a processed oat flour significantly lowered serum cholesterol. The processed oat flours had higher soluble fiber fractions than the less processed oat products.

In a study published in 1983, Rogel and Vohra (Ref. 135) reported no effect from five varieties of oats (oat bran or oat hulls) fed for 4 weeks on the serum cholesterol levels of quail. No data on soluble fiber were given.

Kritchevsky et al. (Ref. 138) evaluated the cholesterol-raising effects of oat and wheat bran on blood cholesterol levels in rats in a three-week feeding study in which semipurified diets containing 0.5 percent cholesterol and 10 percent oat bran, wheat bran or cellulose were fed to male rats. Weight gains varied among the diets. Results showed that, under these study conditions, there were no effects of diet on any of the serum lipids. No data on soluble fiber content of the diets were provided.

Kahlon et al. (Ref. 140) evaluated the effects of rice brans (full-fat or defatted), oat bran, or rice-wheat bran combinations on cholesterol in hamsters. The control diet contained 10 percent cellulose and 0.5 percent cholesterol. Test diets were composed of the control diet plus one of the brans. The oat bran contained 8 percent dietary soluble fiber versus 2 to 3 percent soluble fiber in the other brans. Results showed that rice bran (with fat) and oat bran resulted in significantly lower plasma cholesterol than the control diet. Defatting rice bran resulted in loss of its cholesterol-lowering properties, suggesting that it is the lipid portion rather than the fiber portion of rice bran which is responsible for its cholesterol-lowering effects.

In another study, rats were fed a diet containing 1 percent cholesterol and 0.2 percent cholic acid with added cellulose, oat gum, chitosan, or cholestyramine(5 percent of the diet). Cholestyramine, oat gum, and chitosan all significantly lowered blood and liver cholesterol levels, with the greatest effect with cholestyramine, a commonly used cholesterol-lowering drug. Oat gum, at 5 percent of the diet, reduced serum cholesterol by 23 percent (Ref. 141).

Forsythe et al. (Ref. 142), in a study published in 1978, evaluated the influence of source and particle size of dietary fibers on hypocholesterolemic effects in rats. The sources of fiber were cellulose, wheat, bran, wheat midlings, oat bran, oat flour, sugar beet pulp, soybean hulls and psyIlium seeds. There were significant differences in weight gain and food intake among dietary treatments. No fiber decreased serum cholesterol compared to the fiber-free group.

Significantly lower values of plasma total cholesterol and liver cholesterol in rats fed fiber sources known to contain soluble fibers (oat bran, oat gum, and pectin) compared to rats fed cellulose (insoluble fiber) were reported by Chen et al. (Ref. 143). Rats were fed a base diet containing 1 percent cholesterol and 10 percent by weight of one of the four fiber types. The greater effect of oat gum compared to oat bran was interpreted by the authors to suggest that the plasma and liver cholesterol-lowering effects of oat bran are due to its gum fraction.

Chen and Anderson (Ref. 144) examined the effects of fiber-supplemented diets on total and LDL-cholesterol in rats. Rats were fed one of five experimental diets containing sucrose and 10 percent plant fibers. The diets were as follows: sucrose and cellulose, sucrose-cholesterol with cellulose, sucrose-cholesterol-pectin, sucrose-cholesterol-guar gum, and sucrose-cholesterol-oat bran. Results showed that fiber-fed rats had significantly lowered plasma cholesterol than rats that received cellulose; the lowest concentrations were observed in the pectin-treated group. No data were given on the soluble fiber content of the test diets, although the pectin would presumably contain the highest concentration of soluble fiber.

Chen and Anderson (Ref. 146), in two experiments, examined the effects of guar gum or wheat gum on the plasma and liver lipid levels of rats. In the first experiment, animals were fed one of three diets for three weeks: diet plus sucrose and 10 percent cellulose; sucrose, 15 percent wheat bran, and 4 percent cellulose; and sucrose and 45 percent wheat bran. Each diet provided 10 g of plant fiber. In experiment two, animals were fed one of four diets: diet plus sucrose, sucrose plus cholesterol, sucrose plus cholesterol and wheat bran, or sucrose, cholesterol, and guar gum. The wheat and guar diets provided 7 g of plant fiber; the other two diets provided 4 g of plant fiber. Results from experiment 1 showed that the two wheat bran diets (high in insoluble fiber) significantly raised plasma cholesterol compared to the control. Results of experiment 2 showed the guar diet (high in soluble fiber) significantly lowered serum cholesterol compared to those fed the sucrose-cholesterol or sucrose-cholesterol-wheat bran diets. Plasma cholesterol was similar between the sucrose-cholesterol and wheat groups.

Wilson et al. (Ref. 148) examined the influence of different soluble fibers upon the metabolism of lipids in genetically hyperlipemic, obese Zucker rats. Four diets were tested: a non-fiber diet (no added fiber), a 0 percent soluble fiber diet (cellulose fiber), an oat bran diet (33 percent soluble fiber), and a pectin-citrus fiber diet (100 percent soluble fiber). Except for the control, the fibers provided 10 percent of the total diet weight. Results showed non-significant decreases in total plasma cholesterol in the oat bran and pectin groups compared to the no-fiber and cellulose groups. However, the pectin group (the highest soluble fiber group) had changes in blood lipid components associated with reduced risk of heart disease: significantly lower LDL-cholesterol and significantly higher HDL-cholesterol.

Welch et al. (Ref. 149) evaluated the hypocholesterolemic effects of oat bran fractions. Oat bran was separated into five fractions: oil, insoluble fraction (rich in starch and insoluble fibre), protein-rich, oat gum, and soluble residue. These were fed to chicks. Results showed that, compared to the control, only the diets containing oat bran, oat gum, or the protein fractions significantly lowered plasma cholesterol. Oat gum was the only fraction which had the same effect In reducing plasma cholesterol levels as did the native oat bran. Thus, oat gum was concluded to be the main cholesterol-lowering component of oat bran. Beta-glucan was the main component of the gum fraction, However, the protein fraction also had a beneficial effect on plasma cholesterol levels, although of a lesser magnitude than the gum portion.

Five sources of dietary fiber were compared for their effect on blood and liver cholesterol in beef-fed C57BL/6 male mice (Ref. 150). Mice were fed one of the following fiber supplements (7 percent dietary fiber) with the experimental diet: soybean fiber, rice bran (full fat), oat bran, barley bran, and mixed bran (one-third each of rice, barley, and oat brans). Results showed significantly lower plasma total cholesterol compared to the control in the rice bran and soybean fiber groups.

Ginter et al. (Ref. 151) reported that addition of 5 percent citrus pectin (a high soluble fiber source) and 0.5 percent ascorbic acid to a high-fat diet fed to guinea pigs prevented cholesterol accumulation in blood serum and the liver.

Kakis et al. (Ref. 152) reported reduced serum cholesterol and HDL levels in all psyllium-fed (a soluble fiber) animals as compared to wheat bran-fed (a relatively high insoluble fiber source) animals after a three week experimental period. Relative to the appropriate wheat bran control, psyllium had a graded serum hypocholesterolemic effect that varied from a high of 41 percent at low dietary cholesterol concentrations to 26 percent at high dietary cholesterol concentrations. However, HDL cholesterol (in mg percent and as a percent of total cholesterol), the “beneficial blood cholesterol,” was lower in the psyllium groups than in the respective wheat bran controls. Thus, the overall benefit of psyIlium was not clear from this study.

Life Sciences Research Officers (LSRO) 1982 report to FDA on the health aspects of psyllium seed and other food ingredients (Ref. 153) was submitted with comments. Summaries of studies with beagles fed psyllium-supplemented diets consistently showed lowered serum cholesterol compared-to controls.

2. Animal studies: dose-response relationship between soluble fiber and plasma cholesterol

Shinnick et al. (Ref.134), following evaluation of several approaches to improve the cholesterol-fed rat model used to evaluate the hypocholesterolemic potential of foods, fed nine levels of a high fiber oat flour (HFOF) derived from oat bran to male Sprague-Dawley rats. Ingestion of increasing amounts of HFOF, containing 0 to 10 percent dietary fiber, by rats in which high blood cholesterol levels had been produced with 1 percent cholesterol and 0.1 percent cholic acid, resulted in a significant inverse relationship between serum cholesterol levels and HFOF intake for serum and liver cholesterol levels. Similar results were obtained for liver cholesterol levels. The authors suggested that, although this study does not distinguish among the components of HFOF that may contribute to the cholesterol-lowering effect, the observed dose-response relationship in the rat model is suggestive that larger intakes of soluble oat fiber sources may be accompanied by greater reductions in serum cholesterol levels in humans.

Turley and co-workers (Ref. 147) conducted a dose-response study to three levels of psyllium supplementation in the diets of hamsters. Results were compared to two other nonabsorbable polymers known to have cholesterol-lowering effects (i.e., cholestyramine and surfomer). Animals were fed diets containing 0 percent, 1 percent, 4 percent, or 7.5 percent psyllium. Results showed significantly lowered plasma cholesterol compared to the control group in animals consuming 4 percent and 7.5 percent psyllium. The group consuming 7.5 percent psyllium had the lowest plasma cholesterol, although the authors did not report any significant difference between the 4 percent and 7.5 percent psyllium groups. While all three polymers were effective in reducing plasma total and LDL-cholesterol levels, each exerted different quantitative and qualitative effects on bile acid and cholesterol metabolism, suggesting that mechanisms of action may vary by fiber type.

3. Animal studies: relationship between β-glucan and plasma cholesterol

Three cultivars of hull-less barley containing β-glucans were evaluated for their hypocholesterolemic responses in chickens (Ref. 137). The authors identified the Arizona cultivar of barley as a waxy-starch genotype of high molecular weight and with a high β-glucan content. The Washonupana cultivar was second highest in molecular weight and is also described as a waxy-starch type genotype. The third cultivar, Franubet, has the lowest molecular weight and is not waxy in texture. These latter two genotypes have normal β-glucan contents. Both the Arizona and Washonupana varieties produce highly viscous slurries in water, and this viscosity was greatly reduced by addition of the enzyme, endo-β-glucanase, which destroys the β-glucan. Results of feeding studies in rats showed that both the Arizona and Washonupana cultivars reduce serum cholesterol in chickens. The Franubet variety had no effect. The authors interpreted these results to mean that the cholesterol-lowering properties of the Arizona and Washonupana cultivars were probably a function of their viscous β-glucan content

Klopfenstein and Hoseney (Ref. 139) evaluated the cholesterol-lowering effect of β-glucan-enriched breed. Oat, barley, wheat, and sorghum breads were made with and without β-glucan from each type of grain (e.g., oat β-glucan was processed into oat bread) and fed to rats for 35 days. Breads containing β-glucans from oats and barley adversely affected weight gains and feed efficiencies. Results showed lowered serum and liver cholesterol in rats fed the β-glucan-enriched broad than those fed the control breads. Given differences, in weight gains, results are difficult to interpret.

Fadel et al. (Ref. 145) evaluated the hypocholesterolemic effects of β-glucans in different barley diets fed to chickens and the influence of β-glucanase on the hypocholesterolemic effects. The animals were divided into five groups and fed one of five diets: a corn-diet, Washonupana (WSNP) barley, WSNP with β-glucanase, Fraubet (FNBT) barley, FNBT with β-glucanase. Results showed significantly lowered serum cholesterol only in chicks fed the WSNP diet. LDL-cholesterol levels for all barley fed chicks were significantly lower than that of the corn diet-fed chicks. Only the WSNP fed chicks had serums cholesterol significantly lower than WSNP fed chicks with supplemental β-glucanase. There was no significant difference in total cholesterol in FNBT and FNBT plus supplemental β-glucanase fed chicks, β-glucan in the Washonupana barley has hypocholesterolemic effects and addition of the β-glucanase to this diet reverses the hypocholesterolemic effects. However, the lack of similar finding with added β-glucanase to the Franubet variety suggest a that β-glucans may differ among different varieties.

4. Summary of results from animal studies

The animal studies received as comments, and reviewed above, provide evidence to support the likely effectiveness of soluble fibers relative to the cholesterol-lowering characteristics of diets high in some cereals. However, the animal studies, like the human studies, fail to provide adequate specifications characterizing the test fiber sources Indeed, similarly to many human studies, many animals studies did not analyze experimental diets for soluble fiber content/nor provide descriptions of the physical characteristics or commercial sources of the soluble fibers used as test substances.

Results from the animal studies showing effectiveness of increasing levels of oat products are suggestive, but not conclusive, evidence of a dose response for soluble fiber (Refs. 127, 132, 134). A specificity for the gum portion of oats, the major source of soluble fiber in oats—and specifically, of beta-glucan as the predominant soluble fiber source—is suggested by several studies (Refs. 127, 129, 132, 134, 137, 141, 143, 145, and 149). However, the solubility (and possibly, the effectiveness) of beta-glucan is apparently variable, and can be affected by such factors as plant variety (Refs. 137 and 145), or food processing such as baking of bread (Ref. 154). These results, therefore, suggest that analysis of the beta-glucan content per se may not be sufficient to characterize the active soluble fiber content of foods.

Other soluble fibers were also shown to have serum cholesterol-lowering effects in animals, including pectins (Ref. 128, 143, 144, 148, and 151), psyllium (Refs. 147 and 152), and guar-gum (Ref. 146). However, in the psyllium study (Ref. 152), adverse effects on HDL-cholesterol levels were observed, raising the issue that individual fibers need to be evaluated as to their overall effect on all relevant blood lipid components, not simply limited to blood total or LDL-cholesterol levels. The various fiber sources also appear to have different mechanisms of action and different relative magnitudes of effect (Refs. 128 and 147) , thus suggesting that caution is necessary before generalizing from one type of dietary fiber to another.

C. Conclusions from new studies

FDA reviewed over 40 human studies that became available since publication of its proposed rule, and a number of animal studies submitted as comments. The most commonly studied soluble fiber sources were oat bran, pectin, guar gum, and psyllium. Other fibers studied were wheat germ, beet fiber, and gum arabic. A few studies evaluated the effects of mixtures of soluble and insoluble fibers or food sources of soluble fibers.

FDA evaluated results from these studies in light of studies reviewed in the proposal and conclusions from Federal government and other authoritative reviews. In the proposal, FDA noted that, although most reviews by authoritative scientific bodies had concluded that diets rich in water-soluble fiber fractions were associated with cholesterol-lowering effects in humans, it was not possible to conclude that the observed effects were due to the soluble fiber or to other components associated with consumption of foods rich in soluble fiber. FDA also noted that there was some evidence that different types of soluble fiber have different, effects, and that the analytical measure of soluble fiber may not be adequately predictive of its physiological effects. Thus, FDA concluded that:

> Overall, the available data are not sufficient to demonstrate that it is the total soluble: dietary fiber, or a specific measurable and quantifiable subcomponent, that is related to lower blood cholesterol levels.

(56 FR 60582 at 60592).

The newer evidence available since the proposed rule and reviewed above do not change the conclusions reached by the earlier review. If, however, additional information becomes available to demonstrate that a specific soluble fiber-containing produce a soluble fiber-containing ingredient, or a more highly specified form of foods soluble fiber is effective in lowering blood LDL-cholesterol and does not adversely affect other risk factors for cardiovascular disease (e.g., blood HDL-cholesterol levels), then FDA encourages manufacturers to petition for a health claim for their particular product. The same science will be applicable, regardless of whether the petition is for a single supplement-type product, a clearly specific ingredient or a specific type of soluble fiber contained in foods.

III. Comments

A. Food Claims Versus Nutrient Claims

1. In the proposal on general requirements for health claims (56 FR 60537), FDA specifically requested comments on issues relating to health claims on the label or labeling of foods which targeted foods rather than nutrients, criteria to identify foods eligible for such claims, and possible measures to assure that consumers are not misled as to the benefit of consuming specific products.

A variety of comments submitted in response to the proposed rule on dietary fiber/CVD supported claims on foods. Specifically, relative to a claim for dietary fiber and heart disease, a few comments stated that FDA does have the authority to regulate claims about foods as well as nutrients and that the agency should allow a generic health claim on fruits, vegetables, whole grain and similar types of foods, stating that generous intakes of such foods in diets may help lower the risk of heart disease and certain forms of cancer. Other comments stated that, at this time, a scientific basis does not exist on which to authorize a specific claim for dietary fiber and heart disease, and that a food claim was more appropriate. Other comments suggested that such claims be developed in concurrence with “The Surgeon General’s Report on Nutrition and Health,” (Surgeon Genera’s Report (Ref. 63) and objectives identified in “Healthy People 200: National Health Promotion and Disease Prevention Objectives,” (Healthy People 2000) (Ref. 64), and should focus on the total diet.

A number of comments stated that the amount of fat in the American diet should be lowered and the amount of dietary fiber increased through a variety of food choices from among all the food groups. Several comments favored a limited claim at point of purchase for foods that would help increase dietary fiber intake and lower fat intake. A number of comments noted that an appropriate health statement on food labels should emphasize that eating a variety of food sources of dietary fiber daily (cereals, grains, fruits, and vegetables) can decrease the risk of certain forms of cancer and heart disease. A number of comments stated that food claims, if allowed, should not give the impression that a single nutrient (for example, dietary fiber) is responsible for the reduction in risk of heart disease. Several comments suggested that a health claim regarding dietary fiber and heart disease be made only on fruits, vegetables (fresh or processed), or whole grains and not on products that combine these foods with other ingredients (such as bread products or sauce). Other comments favored use of claims on foods but not supplements.

One comment stated that FDA should allow a fiber health claim because virtually all dietary guidelines for Americans have encouraged consumption of fiber-rich foods, including whole grain cereals, fruits, and vegetables, and that comprehensive government and other reviews by recognized scientific bodies concluded that dietary patterns that include fiber-rich foods are associated with reduced risk of colorectal cancer, heart disease, and other chronic diseases.

As the agency has 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, the agency has concluded that the scientific evidence is sufficient to support a health claim that refers to a substance contained in certain fruits, vegetables, and grain products and relates those foods to a reduced risk of heart disease. Specific reference to the fact that these foods contain soluble fiber is authorized since this nutrient serves as a useful marker for the broad product categories of foods which correlate with reduction in blood LDL-cholesterol levels, and consequently, with reduced risk of heart disease. Thus, the agency has been persuaded by the comments that the totality of the evidence supports a health claim which identifies foods whose use is protective against heart disease and whose selection can be facilitated by reference to the marker nutrient, soluble fiber. Because soluble fiber is usually considered a useful adjunct to, but not a replacement for, a diet low in saturated fat and cholesterol (Ref. 66), the agency is also requiring this information in the label claim.

B. General Comments

2. Several comments supported a health claim for dietary fiber and heart disease, stating that there is sufficient scientific evidence to support such a claim or that a claim is warranted because heart disease and, hence, CVD are major public health problems. Other comments slated that because such a claim would help Americans become aware of the importance of fiber, and because it is well known that population groups who consume high fiber diets have a low incidence of heart disease, these claims should be allowed. Several comments stated that FDA should consider the rapid pace of advances in knowledge that link nutritional substances to good health and disease prevention. Other comments stated that a claim regarding dietary fiber and CVD should not be allowed because overall health depends on a number of factors, such as exercise and lifestyle characteristics.

FDA agrees that CVD and, consequently, CHD are significant public health problems. The agency, in the proposal, tentatively concluded that diets high in fiber-rich foods, including whole grains, fruits and vegetables, are associated with reduced risk of CHD, and thus CVD. In the proposal, the agency also noted that these diets differ in levels of many nutrients, such as saturated fat and vegetable protein, and in types of dietary fiber, making it difficult to ascribe, from observational studies on whole diets, the observed nutrient and disease relationship to a single dietary component (56 FR 60582 at 60592 and 60593).

Several new studies that became available after publication of the proposal were suggestive of positive effects of soluble fiber intakes on blood total- and LDL-cholesterol levels, risk factors for heart disease. However, FDA has also concluded, as noted in the proposal, that the effectiveness of these fibers may be affected by other dietary components (e.g., the level of saturated fat and cholesterol in the diets), as well as by physical characteristics (e.g., particle size or water-holding capacity), or by the fiber source itself. Thus, while the agency has concluded that not ail soluble fibers, i.e., as identified by the AOAC method for soluble fiber determination, are effective in lowering cholesterol, and other components of fiber-rich foods, i.e., vegetable proteins or lipids, may contribute to the cholesterol-lowering effect observed. In addition, the hypocholestrolemic effectiveness of some soluble fibers has been reported in studies in which the source of soluble fiber was consumed as an adjunct to a low saturated fat, low cholesterol, and low total fat diet.

3. Several comments stated that FDA is not following the congressional mandate to consider whether there is significant scientific agreement supporting specific health claims. Specifically, the comments argued that the agency should have placed its inquiry in the proper context by first identifying the range of specific health claims that could be made about dietary fiber and CVD, and then examining the scientific support for each claim.

FDA disagrees with this comment. The 1990 amendments did not require the agency to identify the wide range of health claims that might be made with respect to the 10 topics Identified in the act and then to evaluate all published studies relevant to the claims. Rather, the 1990 amendments instructed the agency to determine whether claims respecting the 10 areas, including “dietary fiber and cardiovascular disease” meet the requirements of section 403(r)(3) or (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 required timeframe. Thus, FDA, in its proposed rule (56 FR 60582), focused its review of the science on those aspects of the dietary fiber and CVD relationship for which the strongest scientific evidence exists: Soluble fiber and CHD.

4. Some comments stated that FDA’s denial of a health claim for dietary fiber and CVD, because of rigid application of a scientific standard higher than that mandated by the 1990 amendments, would have unfortunate public health consequences.

FDA disagrees with the comment that the agency is applying a standard higher than that mandated by the 1990 amendments. To ensure the validity of health claims, Congress enacted a scientific standard in section 403(r)(3)(B)(i) of the act. FDA intends to authorize any claim shown to meet that standard; specifically, any claim for which, based on the totality of the publicly available scientific evidence, there is significant scientific agreement, among experts qualified by training and experience to evaluate such claims, that the claim is supported by the evidence. FDA also disagrees that applying the scientific standard mandated in section 403(r)(3)(B)(i) of the act will have unfortunate public health consequences. FDA believes that for health claims to be truly educational and provide public health benefits, they must be scientifically valid and not misleading. The issue of the scientific standard is discussed in more detail in the final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**.

5. Some comments stated that FDA used disparate criteria in assessing the relationship between lipids and CVD

and dietary fiber and CVD, but did not elaborate on this issue.

FDA disagrees with these comments. In reviewing the scientific literature for the development of its proposed rules for health claims FDA followed the standard mandated by the 1990 amendments.

Federal Government reports and other authoritative documents have consistently concluded that there is a strong relationship between the total amount and types of dietary fat and other lipids in the diet and the risk of heart disease. In developing the proposed rule on lipids and CVD, the agency found that new evidence supported these con elusions. The weight of the evidence showed that diets low in saturated fat and cholesterol are associated with reduced blood total- and LDL-cholesterol and a lower risk of CHD.

In contrast, Federal Government reports and other authoritative documents did not reach similar conclusions that the scientific evidence supported a claim that dietary fiber per se is associated with the reduced risks of CVD. The available evidence showed an association between consumption of diets high in fruits, vegetables, and grain products—diets which are generally high in fiber—and risk of heart disease. For example, in its recommendations in the NAS report "Diet and Health" (Ref. 48), the committee on Diet and Health "agree[d] with most other expert groups in proposing that the intake of vegetables, fruits, and other sources of complex carbohydrates should be increased and that the intake of sugars should be limited." The committee further noted that "the strength of the evidence does not justify making specific recommendations pertaining to dietary fiber at this time. The committee's recommendation to emphasize the consumption of vegetables, fruits, and other sources of complex carbohydrates would, however, indirectly result in increased consumption of dietary fiber."

In developing its proposed rule on dietary fiber and CVD, the agency found that the evidence available at the time the proposal was developed did not alter these conclusions. The agency found that the scientific evidence was not sufficiently conclusive or specific for dietary fiber per se versus other components in the diet to justify use of a health claim relating intake of dietary fiber to reduced risk of CVD.

6. One comment stated that FDA tailed to comply with the 1990 amendments (section 403(r)(4)(C) of the act) in that it has rejected the conclusion of authoritative Federal Government reports without justifying its decision to do so as the act requires. The comment stated that the National Cholesterol Education Program (NCEP) has concluded that soluble fiber may help reduce blood cholesterol levels. The comment refers to the NCEP 1989 consumer pamphlet (Ref. 5), which recommends breads, pasta, rice, cereals, dried peas, and beans, fruits, and vegetables as good sources of complex carbohydrates (starch and fiber). The comment quotes from the pamphlet that these foods are "excellent substitutes for foods that are high in saturated fat and cholesterol. The type of fiber found in foods such as oat and barley bran, some fruits like apples and oranges, and in some dried beans may even help reduce blood cholesterol levels" (Ref. 5). The comment also noted that the NCEP expert panel report, "Population Strategies for Blood Cholesterol Reduction" (Ref. 66), supports the recommendation to consume vegetables, fruits, breads, legumes, and whole grain cereals. The comment quotes the NCEP report that "Dietary fiber supplements are not a panacea for blood cholesterol problems. Foods rich in soluble dietary fiber are, however, a useful addition to a low saturated fatty acid, low fat, and low cholesterol eating patterns* * *" and:

"Oat bran exhibits hypocholesterolemic properties due to its appreciable content of oat gum. Soluble fibers such as pectin, guar gum, locust bean gum, or psyllium in large quantity supplementation have been shown to lower total and LDL-cholesterol levels. The absolute effect on LDL-cholesterol concentrations is modest even when the amount of soluble fiber such as oat bran is consumed in appreciable amounts (60 g). This effect, however, represents a useful adjunct to an eating pattern low in saturated fatty adds and cholesterol" (Ref. 65).

FDA disagrees that, in developing its proposed rule regarding fiber and CVD, it rejected conclusions of Federal Government reports. Comments, through repetition of those portions, of the text. that accompanies dietary recommendations and that includes the words "soluble fiber," are attributing greater significance to the statements relating soluble fiber to heart disease risk than was given to these results by the expert panels. This selected emphasis distorts the meaning of the authoritative reports in question by failing to acknowledge important contributions to reduced risk of disease by the wide variety of nutrients and nonnutritive 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 contributions to reducing risk of chronic diseases.

In the NCEP report (Ref. 65) cited by the comment, the expert panel noted the hypocholesterolemic effects of some soluble fibers, but recommends "a habitual pattern of eating that is consistently low in saturated fatty acids, total fat, and cholesterol," NCEP further recommended that "all healthy Americans recognize that no single food or supplement is the answer to achieving a desirable blood cholesterol level" (Ref. 65). NCEP's recommendation to Americans is to "eat a greater quantity and variety of fruits, vegetables, breads, cereals, and legumes" (Ref. 65). These food choices "will help to meet nutritional needs for minerals, vitamins, dietary fiber (including soluble fiber), and complex carbohydrates, and to replace calories from fat." Thus, the NCEP acknowledges the importance of a dietary pattern that focuses on reducing fats in the diet in order to reduce serum cholesterol. It did not attribute a protective effect from CVD to dietary fiber alone.

Neither the Surgeon General's report on "Nutrition and Health" (Ref. 63), the National Academy of Sciences (NAS) "Diet and Health: Implications for Reducing Chronic Disease Risk"(Diet and Health) (Ref. 48), nor (The Department of Health and Human Services (DHHS)) "Healthy People 2000" (Ref. 64) found the scientific evidence strong enough to attribute the protective effects against CVD of dietary patterns high in fruits, vegetables, and grain products exclusively to the soluble fiber content of such diets. Specifically, the Surgeon General's report on "Nutrition and Health" (Ref. 63) recommends increased consumption of whole grain foods and cereal products, vegetables (including dried beans and peas) and fruits. The report states that:

"the association shown in epidemiologic and animal studios between diets high in complex carbohydrates and reduced risk for CHD and diabetes mellitus is, however, difficult to interpret. The fact that such diets tend also to be lower in energy and fats, especially saturated fats and cholesterol, clearly contributes to this difficulty. Some evidence from clinical studies also suggest that water-soluble fibers from foods such as oat bran, beans, and certain fruits are associated with lower blood glucose and blood lipid levels" (Ref. 63).

The section concludes with the statement. "Current evidence suggests the prudence of increasing consumption of whole grain foods and cereals, vegetables (including dried beans and peas), and fruits" (Ref. 63).

Similarly, the Executive Summary of 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, cereal, and legumes" (Ref. 48). The summary continues "Studies in various parts of the world indicate that people who habitually consume a diet high in plant foods have low risks of atherosclerotic CVD's, 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 Committee does not recommend the use of fiber supplements.

"Healthy People 2000" states that recommendations from the National Cancer Institute, the Surgeon General's report on "Nutrition and Health," NAS' "Diet and Health," and "Dietary Guidelines for Americans" support increased consumption of vegetables, fruits, and whole-grain breads and cereals (Ref. 64). "Healthy People 2000" also states that further research is needed to clarify whether the effect on blood lipids is an independent effect, and if so, to quantify the relationship (Ref. 64).

Therefore, in its proposed decision not to authorize the use on the label or labeling of foods of health claims relating intake of dietary fiber to decreased risk of CVD, the agency's tentative conclusion was consistent with those of Federal Government and other authoritative reports.

FDA's position was also consistent with recommendations in the Institute of Medicine's report "Nutrition Labeling: Issues and Directions for the 1990s" (Ref. 81). In this report, the authors note that:

"there has been a great deal of interest in the specific effects of dietary fiber on several chrome diseases. The strongest argument for an increase in consumption of dietary fiber is the important contribution It makes to normal bowel function. Clear scientific associations of fiber intake with the incidence of heart disease, certain types of cancer, and diabetes mellitus have not been made. One reason may be the difficulty in designing appropriate experiments to specifically test 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, 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 * * *" (Ref. 81).

The Institute of Medicine's report (Ref. 81) also provided specific recommendations, including: (1) "FDA and USDA should require the disclosure of fiber content per serving in grams on the nutrition information panel under the term total dietary fiber"; and (2) "FDA and USDA should discourage labeling of soluble or insoluble fiber contents until methodologies approved by the agencies allow for the adequate and reproducible quantification of the soluble and insoluble fiber contents of a variety of foods" (Ref. 81).

Therefore, FDA is not rejecting the conclusions of these government reports. In its final rule, § 101.76, the agency is permitting a claim relating dietary consumption of fruits, vegetables, and grain products, i.e., good sources of fiber, with reduced risk of heart disease.

7. One comment criticized FDA for misinterpreting the conclusions of the Government of Canada's 1985 "Report of the Expert Advisory Committee on Dietary Fiber" to the Department of Health and Welfare (Ref. 46). The comment stated that the committee expressly advocated health claims for soluble fiber and CHD.

FDA agrees that the Canadian report in question noted hypocholesterolemic effects of some soluble fiber sources, but FDA disagrees that the Department of Health and Welfare supports health claims on soluble fiber in Canada. In its comments to FDA regarding the proposed rule, dietary fiber and CVD, the Canadian Department of Health and Welfare stated its opposition to health messages. Its comment stated that health messages and claims for heart disease and cancer, among other diseases, are not permitted under the Canadian Food and Drugs Act. These diseases are considered to require medical diagnosis and treatment under medical supervision, and thus products bearing messages about them are regulated as drugs. The 1985 report suggested that, if a company desired to use a health claim, then that company should present the evidence of the product's effectiveness based on acceptable test protocols (Ref. 46).

8. One comment stated that FDA failed to note, in the proposed rule, epidemiological studies cited in the NAS' "Diet and Health" that found an inverse association between dietary fiber and CHD, even after adjusting for the possible confounding effects of calories and fat (Ref. 48).

FDA disagrees with this comment. One study was cited, in "Diet and Health" that showed a protective effect of dietary fiber from cereals on risk of CHD independent of caloric intake. Results of a study by Khaw and Barrett-Connor (Ref. 31) (reviewed by FDA in the proposal) found an inverse association between fiber intake and ischemic heart disease mortality independent of calories among other dietary components. However, "Diet and Health" also states that the authors used 24-hour dietary recall to assess intake, a method which has limited applicability in the assessment of the usual dietary intake of individuals in the United States (Ref. 48). Results from the 1982 epidemiological study by Burr (Ref. 82), also cited in "Diet and Health," showed a lower risk of CHD in 10.943 vegetarians than in nonvegetarians, but their decreased risk could not be accounted for by increased fiber consumption, because many other components of the diet also differed between these two groups. Therefore, FDA did not misinterpret the conclusions of "Diet and Health" that there is no conclusive evidence that it is dietary fiber, rather than other components of fiber-rich foods, that reduces risk of CVD.

9. One comment disagreed with the indication in the proposed rate that a "risk/benefit" argument was not a sufficient or appropriate basis on which to authorize a health claim for food labels. The comment stated that, although the data for dietary fiber do not support the hypothesis for reduced risk of CVD, the "potential benefits far outweigh the potential disadvantages."

FDA disagrees with this comment. Congress enacted a scientific standard for health claims in section 403(r)(3)(B)(i) of the act. Claims must meet the statutory requirements; that is, based on the totality of the scientific evidence, there must be significant scientific agreement, among experts qualified by training and excellence to evaluate such claims, that the claim is supported by such evidence. The concept of "potential benefits outweighing potential disadvantages" is not an acceptable substitute for the scientific standard mandated by Congress.

C. Specificity of the Relationship Between Soluble Dietary Fiber and Heart Disease

10. Several comments stated that FDA's refusal to authorize a health claim on dietary fiber and CVD is based

on the agency's determination to treat all dietary fiber as a group, rather than considering each fiber source individually. The comment stated that dietary fiber is composed of a diverse group of materials, as the agency observed, and each has its own physiological effects The comment noted that certain water soluble-fibers have been documented to reduce serum cholesterol, thereby lowering the risk of CHD.

FDA disagrees with this comment. In the proposed rule (56 FR 60582), FDA limited its review of the science to those aspects of the dietary fiber and CVD relationship for which the strongest scientific evidence exists: soluble dietary fiber and CHD. FDA also noted, however, that soluble fiber was a heterogenous family of fibers which vary in both chemical, and physical characteristics. After reviewing the totality of the evidence, the agency is persuaded that even if soluble fiber alone is effective in reducing risk of heart disease, greater specificity than that identified by existing analytical methods is needed in order to predict the effectiveness of soluble fiber in foods.

11. LSRO submitted its document, "Dietary Fiber and Cardiovascular Disease" (Ref. 40), as a comment. In this final report, LSRO stated that it remains to be determined whether the observed effects of dietary fiber on serum cholesterol reduction result strictly from the fiber or from other components of the fiber-rich food or from a combination of these factors. The report stated that studies suggest that soluble fiber, a specific type of dietary fiber, is hypocholesterolemic, while insoluble fiber is not. Further, when foods are used, foods rich in β-glucans seem to have a more hypocholesterolemic effect. The report states that there is no indication of optimum level or even a dose-related effect, and notes that there are suggestions as to optimum level of intake for "better health" (e.g., normal bowel function) but not for prevention of disease. In addition, there are no data relating to transience of fiber effects, although this is amenable to experimental testing. The LSRO report also noted that generalization to the U.S. population is difficult. Presumably, persons at high risk, such as those with a family history of hyperlipidemia or heart disease, would benefit most.

The LSRO report also states that it is unclear whether the lipid-lowering effects observed in some studies are the result of the fact that most high fiber diets are low in fat. According to the report, most of the available evidence suggests that isolated polysaccharides, such as pectin, guar gum, locust bean gum, oat gum, and psyIlium mucilliod, have the ability to lower serum cholesterol levels; however, there are no data to indicate that a fiber present in a food is the same as when it has been extracted and purified. The data suggests that diets high in fiber-rich foods can influence lipidemia, but this effect is probably due to overall changes in the diet caused by the addition of fiber sources rather than simply to a direct effect of fiber.

One comment stated that FDA failed to cite LSRO's (Ref. 39) conclusions regarding hypocholesterolemic effects of some soluble fibers.

FDA agrees that the results of clinical studies suggest that soluble fiber is hypocholesterolemic, while insoluble fiber is not. FDA also agrees that the effect of fiber-rich foods on serum lipids is related to the total diet, i.e., one that is low in saturated fat and cholesterol and high in soluble fiber-rich foods, such as vegetables, fruits, and grain products.

FDA disagrees that the agency failed to consider the conclusions of this report. Both of LSRO's reports (Refs.39 and 40) concluded that soluble fibers were related to reduced blood cholesterol levels, but the LSRO report (Ref. 40) also concluded, as noted above, that it remains to be determined whether the observed effects of dietary fiber on serum cholesterol reduction result strictly from the fiber or from other components of fiber-rich foods or from a combination of these factors. Data available since LSRO's report (Ref. 40) provided some additional information as to the effect of soluble fiber and blood cholesterol reduction.

12. One comment stated that FDA failed to note part of the World Health Organization's (WHO) report (Ref. 71) oil the relationship between soluble fiber and blood cholesterol levels (and hence CHD). The comment quotes the report, "[o]ther dietary components, such as dietary fibre, have an effect on serum cholesterol in experimental studies and are correlated in intercountry comparisons. As with fatty acids, the different forms of dietary fibre may have different effects on serum cholesterol" (Ref. 71). The comment concludes that, although the WHO report did not analyze the relevant science, it acknowledges the evidence that soluble fibers have hypocholesterolemic effects.

FDA disagrees with the comment that it failed to note the WHO statements regarding soluble fiber. Although the WHO report states that "different forms of dietary fiber may have different effects on serum cholesterol," it does not identify which form of dietary fiber affects serum cholesterol; the term "soluble fiber" was not used in the report (Ref. 71).

13. Several national health organizations with expertise in heart disease agreed with FDA's proposed conclusion, that, at this time, there is insufficient evidence to link dietary fiber, per se, to CVD. The comments stated that the proposal is consistent with the conclusions of all previous expert groups. The comments stated that the association between fiber and blood lipids is specific to soluble fiber and that specificity to fiber class la unresolved. The amount of soluble fiber necessary to produce blood cholesterol lowering is unclear; nor is it known whether (and if so, how much) the response differs by type of soluble fiber (i.e., β-glucan versus pectin). Furthermore, the comments state that FDA's review of the scientific literature (56 FR 60574) mentions the tumor-enhancing effect of soluble fibers in animal studies. They recommended that FD. not allow health claims that link fiber to risk of CVD's. The comments stated that there are insufficient data to warrant such a claim and that it is misleading to permit a claim that singles out a particular food or foods in diets. The comments stated that if there were sufficient data to make a claim, it should be stated in the context of a low fat, low cholesterol diet. It would also be necessary to specify the type of fiber, e.g., soluble fiber, in the case of CVD.

FDA agrees that a health claim for a dietary component should be stated for the context of the total daily diet and, in this case, should be specific to the type of dietary fiber. The agency has been persuaded, based on its review of the comments and its review of the scientific literature, that questions remains as to whether the cholesterol-lowering effect observed with some soluble-fiber food source (e.g., oats) is due to the soluble fiber component or to a combination of other components associated with these foods.

14. One comment questioned the motivation behind the agency's tentative rejection of health claims for fiber and CVD. The comment stated that FDA does not want any health claims on dietary supplements and that the agency should not preclude claims because of concern that dietary supplement manufacturers will then be able to make such claims. Comments from supplement manufacturers stated that, if health claims are permitted on fiber-containing foods, then fiber supplements should also be permitted to carry a claim because there is no difference between fiber in foods and

fiber in supplements and all fiber supplements are safe. Other comments stated that FDA should authorize health claims on supplements because supplements offer an alternative to consumers who might otherwise not eat sufficient amounts of fiber in their diets.

FDA disagrees with the comment that it does not want health claims on fiber supplements and with the suggestion that it rejected dietary fiber and CVD health claims because of concern that supplements manufacturers would then be allowed to make such claims. FDA has applied the law equally to supplements and conventional foods.

As the agency's proposed rule stated, FDA proposed to deny a health claim for dietary fiber and CVD because the agency tentatively concluded that the available scientific evidence was not sufficiently conclusive or specific for dietary fiber per se. FDA notes that the comment claimed that there is no difference between fiber in foods and fiber in supplements but submitted no data were submitted to support this statement. Indeed, several expert reports (Refs. 39, 40, and 46) concluded that there is no evidence that fiber, when isolated and/or processed in foods, has the same physiological effects on serum cholesterol as consumption of the native fiber from fiber-rich foods. These reports note that the predictive capability of analytically determined values for soluble fiber and physiologic activity has not been established, and effectiveness may vary by source of fiber or by physical characteristics not detected with chemical methods of analysis (e.g., particle size or water-holding capacity). They also note that safety may vary between native and isolated sources of fiber.

D. Comments Regarding a Relationship Between Specific Soluble Dietary Fibers and CVD

15. One comment submitted a review of available literature for particular fibers. The comment stated that several of these fibers are "effective as cholesterol lowering agents and in addition, they are safe to use provided a few reasonable precautions are taken." The comment identified fibers such as locust bean gum, guar gum, oats, pectin, and psyllium mucilage as materials with hypocholesterolemic effects. Less well-tested fibers that have some hypocholesterolemic effects (for example, barley, acacia gum, dried beans, and karaya gum) were also mentioned. The comment stated that wheat fiber requires more study to determine its effects. The comment notes that, since dietary fiber represents a diverse group of materials, FDA should consider allowing health claims and statements on individual dietary fiber materials. The comment also recommended separate health claims on fibers with "hypocholesterolemic" activity, because each of these fiber materials also has a different dose-response. The comment provided some criteria on which to base the individual fiber claims.

FDA agrees that the scientific literature shows that dietary fiber is a complex group of dietary substances with differing chemical, physical, and physiological properties, and that not all soluble fibers are alike in their hypocholesterolemic properties. FDA disagrees with the recommendation to allow individual health claims on various soluble fibers, but does concur that the effectiveness of individual fibers in foods may be documented for specific food products or for fibers whose physical and chemical characteristics are well specified (e.g., oat brans meeting specified parameters). Thus, if manufacturers can document. through appropriate studies, that the soluble fiber in their particular food is effective in lowering LDL-cholesterol, and has no adverse effects on other heart disease risk factors (e.g., HDL-cholesterol), then FDA encourages manufacturers to petition for a health claim for their particular product or ingredient. Additionally, if new evidence becomes available which more clearly identifies what type of soluble fiber is effective, this also would be appropriate for a petition.

16. Another comment stated that part of FDA's difficulty in interpreting data on dietary fiber and CVD results from the consideration of soluble fiber as a single nutrient instead of as a class of diverse substances. The comment stated that data exist to support at least one soluble fiber, β-glucan, as the substance responsible for the majority of the cholesterol-lowering effects observed with some fiber sources. Another comment stated that there is a preponderance of literature supporting oat bran and its hypocholesterolemic effects and that the active mechanism behind oat bran's effectiveness is the β-glucan component. The comment suggested that the agency allow foods to be identified that contribute to eating patterns that reduce the risk of disease.

FDA agrees, as discussed in the proposal, that dietary fiber is a diverse group of substances and not all soluble fibers are alike in their hypocholesterolemic properties. FDA also agrees, based on new data submitted as comments, that there is evidence to suggest that β-glucan has hypocholesterolemic properties. However, as noted in the meta-analysis (Ref. 125), other components of oats, such as tocotrienols and oat oil, may play a role in the reduction of blood LDL-cholesterol levels. However, FDA is authorizing a claim on fruits, vegetables, and grain products—foods that are good sources of soluble fiber and other substances that may have cholesterol-lowering properties.

17. Comments from a health professional organization stated that several studies have shown that soluble fibers, such as those in oat, beans, psyllium, and guar, appeared to lower serum cholesterol, at least when given in large amounts. The comment further stated that weight loss observed in some studies may possibly be far more important than fiber in contributing to cholesterol reduction.

FDA agrees that weight loss associated with test diets may affect the ability to differentiate between the effects of the test substance (i.e., soluble fiber) versus the well-documented effect of weight loss on blood total- and LDL-cholesterol. This was discussed in the meta-analysis submitted as a comment (Ref. 125). Several studies observed reductions in blood cholesterol levels in studies in which loss did not occur. For example, in a study by Marlett et al. (Ref. 124), submitted with another comment, there was no significant weight loss in either the control or soluble fiber (oat bran) groups during the fiber intervention period. Serum cholesterol was significantly lower in the oat bran group than in the control group. Spiller et al. (Ref. 87) reported no weight changes in two groups receiving either guar gum or oat fiber. Both groups experienced significantly lowered serum cholesterol. In two other studies (Refs. 118 and 120), there was no significant difference in the weight loss between subjects consuming oat bran (Ref. 120) or psyllium cereal (Ref. 118) and those consuming wheat bran. The oat bran group had significantly lower serum cholesterol than the wheat group and compared to the control period. Thus, while the agency agrees that weight loss may be a confounding factor, the new evidence is consistent with the concept that consumption of diets high in certain soluble fiber-rich foods, independent of body weight, has a beneficial effect on blood cholesterol levels.

E. Comments Regarding FDA's Interpretation of Specific Studies

Some comments cited references that were already reviewed by FDA or the consensus documents, or were studies of questionable relevance to human CVD (e.g., studies evaluating postprandial glucose response of fiber diets). Some abstracts were also cited that do not provide sufficient information for evaluation. Review articles that provided no new data were also included with some comments.

18. One comment stated that the study by Kahn et al. (Ref. 25) showed significant decreases in relevant parameters in the test groups versus baseline and that the authors concluded that soluble fiber "appears to be quite effective" in lowering those parameters. In the proposed rule, FDA reported that there was no significant difference in serum cholesterol between the test group and the control group.

FDA notes that it did report that a significant difference in serum cholesterol existed between baseline and intervention values if the results are examined without consideration of the immediate versus delay constraint of the design. The agency initially concluded that the study did not support an effect of oat bran on serum cholesterol lowering because of the lack of statistical significance when examining only the difference between the immediate intervention group and its control. FDA believes that the study design should have been modified to overcome the problem of the time delay in comparing the groups. However, after further review, FDA agrees with the authors (Ref. 25) that, after correcting for the time delay, the study does show that oat bran supplementation reduced serum cholesterol.

19. One comment criticized FDA for calling a "p value" of 0.052 in the paper by Anderson et al. (Ret. 5) "nearly significant." The comment suggested that a more precise term would be "borderline significant."

FDA acknowledges that the term "borderline significant" is more commonly used professionally, but considers that this does not negate the need for caution in reviewing the results of this paper.

20. One comment stated that FDA failed to report the modest effect, from a study by Bell et al. (Ref. 12), of a pectin-enriched cereal on serum cholesterol.

FDA disagrees with this comment. Of the two fiber-enriched cereals (one enriched with psyllium and the other with pectin) tested by Bell et al. (Ref. 12), FDA reported that only psyIlium demonstrated a significant reduction in cholesterol. The agency correctly stated that the psyllium-enriched diet demonstrated significant lowering of total- and LDL-cholesterol but that the pectin did not.

21. A comment disagreed with FDA's statement that the study by Davidson et al (Ref. 15) did not demonstrate significant reductions from baseline levels in total cholesterol with daily intakes of up to 2 oz of oatmeal (1.2 to 2.4 g β-glucan/day) or 1 oz oat bran (2.0 g β-glucan/day) in persons on a Step 1 diet.

FDA correctly reported that only the higher fiber intake groups showed statistically significant effects. The small sample size may have prevented seeing an effect in the lower doses. FDA agrees that, based on the results of this study, an intake of soluble fiber (in this case, β-glucan from oats) of about 3 g per day or more was beneficial in that it resulted in a significant lowering of serum cholesterol in persons consuming a low-fat diet.

22. A comment asked FDA to consider a result from a study by Newrnan et al. (Ref. 50) which used β-glucan from barley and compared it to wheat fiber. The cholesterol levels of the high β-glucan group did not differ significantly from baseline after four weeks. The author explains this lack of significance by citing the small sample size and small amounts of β-glucan consumed.

FDA does not necessarily disagree with this comment, but considers that it was correct in not assessing the results as positive (i.e., a true difference exists) because a statistically significant effect was not demonstrated.

23. One comment stated that FDA failed to consider significant the results by Van Horn et al. (Ret 68). In this study, the investigators tested the effects of oat-bran intervention on serum cholesterol levels in subjects with normal or mildly elevated serum cholesterol levels. The authors reported a difference ($p = 0.074$) in serum cholesterol between the oat group and the control after 8 weeks.

FDA did not consider this result significant because the small sample size was not a problem in this study and the p values reported are one-tailed. Such values allow leeway over the more conventional and conservative two-tailed tests.

24. One comment stated that FDA did not properly interpret the results of a study by Mclntosh et al. (Ref. 44), which compared the cholesterol-lowering effect of β-glucan from barley to that of wheat fiber.

FDA disagrees with this comment. Although there was a significant difference between cholesterol levels of the two groups, this was largely due to a rise in total cholesterol that occurred in the wheat group compared to baseline. In this case, it is not possible to know whether wheat acted as a placebo, or whether wheat itself is cholesterol-raising. However, because the group fed barley did not show a significant lowering of cholesterol from their own baseline level, the agency does not find that a positive effect of barley was demonstrated.

25. Another comment addressed a study by Burr et al. (Ref. 13) that examined whether there was a change in mortality rates between men given dietary advice to increase fiber intake or to reduce fat intake. The comment was specifically concerned with FDA's conclusion that the study was not able to show a difference between mortality rates in the two groups. The comment stated that the results show that increasing fiber intake is no less effective than decreasing fat intake in the prevention of CHD.

FDA disagrees with this comment. Because there was no group in this study which acted as a control (no changes in diet), the study does not provide evidence that either diet in the studies is effective or that neither is effective. The agency finds that the study does not add to the evidence of the effects of fiber.

26. One comment stated that a study by Little et al. (Ref. 42) that shows that lowering fat is responsible for significant lowering of total cholesterol, while increasing fiber is not, did not specify the type of fiber (i.e., soluble versus insoluble) and should not be considered as part of the fiber-CHD evaluation.

FDA disagrees with this comment. The agency considered any fiber study which might be relevant to the health claim. However, the weight given to study results was influenced by several factors, including the quality and usefulness of the information on soluble fiber intakes.

27. One comment noted that the study by Demark-Wahnefried et al. (Ref. 16) showed a significant drop in total serum cholesterol in all three of the following dietary groups. A high fiber, low-fat diet; a low-fat diet alone; and a regular diet with fiber added. The comment contended that, because there was no significant difference between any of the groups, this study showed that increasing soluble fiber intake is as effective as reducing fat intake.

FDA disagrees with this comment. This study does not support a conclusion that soluble fiber is as effective as reducing fat intakes. These results showed that the cholesterol-lowering effect of a low-fat diet was not further enhanced by the addition of fiber. Additionally, there was a significantly decreased consumption of fat and cholesterol in all groups; this is consistent with the hypothesis that fat displacement is one mechanism by which high fiber diets lower total cholesterol.

28. Another comment also criticized FDA's review of the Demark-Wahnefried et al. study (Ref. 16). The comment stated that, according to the Keys equation for predicting changes in blood cholesterol levels from changes in intakes of fatty acids, only 40 percent of serum cholesterol's lowering is explained by changes in dietary fat.

FDA disagrees with this comment. The agency's evaluation of this study pointed out the lack of significant difference between cholesterol lowering on the regular diet plus oats or the low fat, low cholesterol diets. The study did not estimate how much, if any, of the remaining 60 percent is attributable to oat bran.

29 One comment stated that FDA misinterpreted the results of the study by Keenan et al. (Ref. 26) by failing to note that the control group decreased its soluble fiber intake over the study period, thus accounting for the return to baseline for serum cholesterol in this group by the end of the study.

FDA disagrees that it misinterpreted the results of this cross-over study, in which the authors compared the hypocholesterolemic effects of oat- or wheat-supplemented Step 1 diets with a control group on the Step 1 diet only. Although FDA recognizes the problem with the control group, the agency correctly reported that there was a lack of significance in the change in serum cholesterol in the oat-wheat group during the oat phase. Recognizing that the control group decreased its soluble fiber over the study period may suggest redoing the study with a better control of soluble fiber in this group.

30. Another comment also disagreed with FDA's criticism that the study by Keenan et al. (Ref. 26) did not have a placebo. The comment stated that the wheat group was considered a placebo because it has been well documented that wheat has virtually no cholesterol lowering properties. A similar comment was made regarding FDA's criticism of a study by Swain et al. (Ref. 57) in which wheat was also used as a placebo.

FDA has expressed concern about the use of wheat as a placebo due to its inconsistent effect on serum cholesterol in some reports. Although the study by Keenan demonstrated an increased total cholesterol in the "oat-wheat" group of 6 percent above baseline during the wheat period, in Swain's study the wheat group showed a 7 percent decrease in serum cholesterol. Based on these studies and1 other reviews, FDA now believes that these variations in serum cholesterol may be a function of the amount and method of administration of the wheat and must be reviewed with caution. Rather than discounting the use of wheat as a placebo, FDA believes that the placebo, whether it is wheat or another fiber, must be evaluated individually for each study.

31. One comment suggested that the FDA failed to note that the study by Davidson et al. (Ref. 15) was specifically designed to determine whether β-glucan has a dose-response effect on serum cholesterol after reducing and controlling for fat intake. Subjects in this study consumed a Step 1 diet with two levels of oat bran incorporated into the diet. FDA disagrees that it failed to note this point. The authors of the study stated that there is a "lack of continued dose response" (Ref. 15). In addition, the authors say that "the impact of fat substitution on serum cholesterol reduction with oat cereals cannot be completely excluded" due to the lack of isocaloric control for the higher-dose treatment groups (Ref. 15).

32. Another comment on the Davidson et al. study (Ref. 15) stated that FDA's criticism of the lack of a control group was not valid due to the 6-week wash-out period. The comment states that, during this wash-out period, the serum cholesterol values of all treatment groups returned to baseline levels, suggesting that the hypocholesterolemic effects observed were the result of oat β-glucan supplementation.

Although the wash-out period is not the equivalent to a true control, FDA agrees that, considered with the evidence from the intervention period, the decrease in serum cholesterol suggests an effect of β-glucan at the higher levels of intake.

33. One comment criticized FDA for failure to note regarding the study by Bell et al. (Ref. 11) that the psyllium group on the Step 1 diet had significant reductions in total cholesterol levels as compared to the placebo (wheat fiber) controls.

FDA disagrees with this comment. The problem with this study is that, during the second 8-week test period, the psyllium group's total cholesterol had risen to only 1.5 percent below the baseline level. The significant difference still exists between placebo and test group because the mean serum cholesterol level of the placebo group actually increased to a level higher than baseline. The agency believes that these results weaken the support for cholesterol-lowering effectiveness over time on this diet.

34. One comment stated that the study by McIvor et al. (Ref. 45), showing no effect of guar gum on serum cholesterol in a population of overweight noninsulin dependent diabetics, should not have been discussed in the proposed rule. The comment explained that this was not a typical population group (diabetics consume large amounts of fiber products to help with carbohydrate metabolism), and the objective of the study was to test the safety of guar. In addition, the comment states that the diets were uncontrolled so the results could be confounded by additional fat from the granola-type bars in which the guar gum was incorporated.

PDA disagrees with this comment. Although overweight diabetics may not be a typical group, FDA did not eliminate the noninsulin diabetics from the criteria for evaluating fiber studies; insulin-dependent diabetics are excluded, however. Although the objective of the study was not to evaluate cholesterol-lowering effects, this information was presented and FDA considered it to be relevant. In addition, adding fiber to a diet without changing the overall diet is probably a very typical form of consumer behavior. The agency also notes that it did not say that fiber intake had no effect in this study, but rather that the results are "inconclusive."

35. One comment addressed FDA's review of the study by Lo and Cole (Ref. 43), in which pooled periods only show a significant difference between the placebo and soy fiber groups. The comment stated that the placebo's effects on total cholesterol were insignificant, while soy's effects were significant.

FDA disagrees with this comment. As shown in table IV of the paper, the 2 percent decrease in serum cholesterol reported after soy fiber consumption in Group B is not significant. FDA questions the inconsistency of the results (i.e., after the placebo effect is gone, is Group B more representative of the effect?). The order of treatment effects on the results should have been considered in the conclusion.

36. One comment criticized FDA's review of the study by Superko et al. (Ref 56), which FDA discounted as demonstrating significant differences between fiber groups. The comment stated that FDA has failed to consider the significant reductions in serum cholesterol levels between baseline and test group consuming guar gum.

FDA disagrees with this comment. While it is true that at 4 weeks them was a significant difference between total cholesterol levels from baseline, at 8 weeks the p value dropped to 0.15, which is not statistically significant. When FDA calculated the difference between the placebo to guar supplementation at the 4 and 8 week intervals, neither was significant as defined by a p value of 0.05 or less.

37. One comment stated that FDA incorrectly reported results in the study by Beling et al. (Ref. 10). The comment stated that FDA reported nonsignificant reductions in serum cholesterol between the group using oat-enriched cereal and the control group.

FDA agrees with this comment. After reexamining the results, FDA notes that they show a significant difference between the two groups, thus adding support to a cholesterol-lowering effect of soluble fiber-rich foods in combination with consumption of a low-fat diet.

38. Another comment stated that the weight loss differences reported in the study by Beling et al. (Ref. 10) were not significant between groups, so effects of weight change should be similar. The comment also stated that it is not possible to completely "blind" a study that uses ready-to-eat cereal.

FDA agrees with the comment.

39. One comment stated that FDA criticized the lack of baseline fiber intake data in the study by Gold and Davidson (Ref. 19), but did not explain the significance of that assertion.

FDA considers baseline fiber intake data necessary to determine if the effect seen could have resulted from fat displacement in the diet.

40. One comment criticized FDA's evaluation of a study by Stewart et al. (Ref. 55) and stated that FDA failed to consider the effect after adjustment when reporting the study as nonconclusive of an effect. The study by Stewart and colleagues (Ref. 55) noted that the psyllium supplement administered had a nonsignificant effect on total serum cholesterol when dose was not considered, but a significant effect after adjusting for dose.

FDA disagrees with this comment. Referring to both Figure 1 and Table 4 in the study, the linear trend is driven by the higher dose values, which have very small numbers compared to the overall study population. In addition, the author has excluded the 739 control subjects in the dose-specific analysis for a dose of 0 (no psyllium intake), which, if included, would most likely eliminate any trend. The results of the study do not support any overall effect of psyllium on serum cholesterol.

41. One comment slated that FDA unnecessarily distinguishes studies using separate fiber supplements from those using fiber-enriched foods.

FDA disagrees with this comment. FDA is applying a consistent legal standard to its consideration of studies on fiber supplements and studies of fiber-rich foods. However, from a scientific standpoint there is reason to believe that the use of fiber at higher intakes and higher concentration (i.e., a fiber supplement taken as a single dose prior to meals) may well differ from the typical intake of fiber from foods (i.e., smaller amounts of fiber consumed throughout the day). If an effect is seen when fiber is consumed at higher intakes and higher concentrations, it cannot be assumed that there is a linear dose-response effect that will translate into significant effects at more usual levels of intake. Conversely, if an effect is seen when fiber is consumed with more typical intake from foods, it may not automatically translate into an effect from fiber supplements. Additionally, isolated fibers (as used in supplements) may vary in chemical and physical characteristics from native or less processed fibers. Since a mechanism of action for soluble fiber in reducing blood LDL-cholesterol levels has not been identified, it is possible that processing of soluble fibers may affect their ability to lower blood cholesterol levels.

F. Comments Regarding Applicability to the General Population/Public Health Aspects

42. One comment criticized FDA for including, in the dietary fiber-CVD proposal, the criterion that studies must be conducted in persons who generally represent the healthy U.S. population, i.e., adults with cholesterol readings below 300 mg/dL. The comment stated that this criterion eliminated many valid studies that demonstrate significant scientific agreement for a claim about the relationship between soluble fiber and CHD; and secondly, that these studies remain useful to demonstrate soluble fiber's hypocholesterolemic effects at lower doses, for longer durations, in conjunction with reduced-fat diets.

FDA agrees that populations at higher risk may provide a more sensitive group for identifying a nutrient/disease relationship. However, extrapolation of results from a high risk group to the general population must be done with caution and generally requires some confirmatory studies in the general population. FDA included, in its review, studies on persons considered to be at high risk, i.e., with levels of blood total cholesterol between 200 and 300 mg/dL. FDA, thus, included a large segment of the general population whose risk levels fall in this range, but excluded the much smaller segment of persons with blood total cholesterol levels above 300 mg/dL, because these people often have multiple and serious health problems, making it difficult to generalize results beyond the particular study populations. According to the National Center for Health Statistics (Ref. 79), only 5 percent of the U.S. adult population of men and women have serum cholesterol levels 300 mg/dL or higher. Results of two studies (Refs. 9 and 59) showed that subjects with a mean serum cholesterol level ≤300 mg/dL had significantly lowered serum cholesterol at the end of the test period compared to baseline. Final serum cholesterol levels, however, was still greater than 300 mg/dL. Thus these individuals remained severely hypercholesterolemic and at high risk for CVD.

It is also important to note that the hypocholesterolemic effect in these two studies (Refs. 9 and 59) and many of the other studies attenuated with time, and serum cholesterol levels increased toward baseline. Thus, the agency does not agree with the comment that such results are necessarily useful to demonstrate a long-term hypocholesterolemic effect of soluble fiber at lower doses. Interpretation of results depends on how well compliance with the test regimen was accomplished.

Of the other 33 studies reviewed in the proposed rule (56 FR at 60596 through 60609), the mean blood total cholesterol was in the mid- to upper-200's (mg/dL) because many of the subjects had individual serum cholesterol levels greater than 300 mg/dL. These studies were included in the evaluation of the relationship between dietary fiber and CVD if they met the other evaluation criteria.

43. Another comment criticized FDA for separately evaluating studies using "typical" or "usual" American diets (i.e., approximately 37 percent of calories from fat) and those using a reduced fat (Step 1) diet. The comment stated that the agency should have given equal weight to studies whether they involved a "typical" American diet or a reduced fat (Step 1) diet.

FDA disagrees with this comment. As stated in the proposed rule (56 FR 60582 at 60587), "Responses of blood cholesterol levels to dietary treatment are affected by many factors, including initial (baseline) blood cholesterol levels and dietary factors (i.e., the level of saturated fiat and cholesterol in the diet)." Because serum cholesterol is responsive to dietary intakes of saturated fat and cholesterol, FDA separated the studies on the basis of whether fiber effects were being evaluated as part of a typical American diet or as part of a reduced fat diet.

Results of fiber studies become confounded when the test diet is not adequately controlled, or not assessed at all, and when subjects make their own changes to their diets by consuming less total and saturated fat. In such cases, the true effects of fiber, if any, cannot be adequately determined. Although the agency grouped studies based on type of diet, it did give them equal weight based on the evaluation-criteria.

44. One comment stated that FDA failed to consider studies reporting only modest reductions in serum cholesterol as strong evidence of soluble fiber's effectiveness. The comment refers to the public health significance of even a small reduction in serum cholesterol; i.e., a 1 percent reduction in serum cholesterol levels predicts approximately a 2 percent reduction in CHD(Ref.41).

FDA disagrees with this comment. FDA recognizes that changes in serum cholesterol in fiber-feeding studies are generally small. However, if, due to the sample size of the study, this change is not sufficient to demonstrate statistical significance beyond that which may occur by chance (generally accepted by epidemiologists and biostatisticians as $p<.05$), it cannot be concluded that a true effect has been observed.

45. Another comment stated that there is no scientifically valid basis for excluding studies involving subjects whose blood cholesterol levels exceed 300mg/dL.

FDA disagrees with this comment. As stated above, 5 percent of the U.S. population have serum cholesterol levels greater than 300 mg/dL (Ref. 79). It is important to remember that "the magnitude of plasma lipid response is frequently related to the initial plasma lipid status of the experimental subjects. Persons with higher plasma lipids initially usually experience the greatest plasma lipid response to diet intervention" (Ref. 33). What may cause an effect to look significant may be driven largely by the magnitude of the change, which is more likely to be observed in those individuals with very high serum cholesterol levels. To base conclusions on one group that will respond to a much greater extent than another is misleading as to those persons with normal to moderately elevated serum cholesterol levels, who comprise 95 percent of the adult population.

46. One comment noted that population compliance was essential to the success of dietary intervention for improved public health and that adding fiber to the diet is more acceptable to consumers than removing fat.

FDA agrees that compliance is an important factor, but, with respect to fiber and CVD, it must first be established that addition of fiber alone to the diet is an effective means of reducing serum cholesterol.

G. Comments Regarding Issues of Study Design, Confounders, Fat, etc.

47. One comment stated that FDA criticized studies that do not control for the effects of low dietary fat when examining increased dietary fiber consumption and cholesterol reduction.

FDA disagrees with this comment. Although many studies provide compelling evidence of the effect of a combined low-fat, high fiber diet on lowering serum cholesterol, FDA examined the scientific evidence to determine whether a specific relationship existed between soluble dietary fiber and risk of heart disease, and whether sufficient scientific evidence was available to support a health claim for dietary fiber and heart disease.

48. Another comment criticized FDA's evaluation of a study by Van Horn et aL (Ref. 67) for inappropriately discounting the correlation of fiber intake with serum cholesterol by pointing out that many other nutrient intakes besides fiber showed correlations with cholesterol levels. The comment stated that dietary fiber had correlations with CHD that were as statistically significant as those for fat and CHD, and this argues for a finding that significant scientific agreement supports a claim about the relationship between fiber and CHD.

FDA disagrees with this comment. FDA again emphasizes that many other nutrient intakes in addition to dietary fiber show statistically significant correlations. In a cross-sectional survey analyzed in this manner, one of the first things that must be considered when many factors show significance is whether they are highly correlated with each other. If this is the case, displacement of fat in the diet by fiber is one explanation for the observed effect.

49. Another comment argued that, although FDA has stated there may be other micronutrients or components in vegetables, cereal, fruits and berries other than soluble fiber that may have contributed to the cholesterol-lowering effects of some soluble fiber-containing foods, the agency has failed to identify them.

FDA agrees that it did not identify other components in foods that may have serum cholesterol lowering effects. Its point in this statement was that attribution of effects to soluble fiber per se, when foods contain a wide range of vitamins, minerals, and other substances, is misleading. The authors of the meta-analysis (Ref. 125) also noted that other components of oats may play a role in the cholesterol-lowering properties observed in human studies.

50. Another comment criticized FDA's evaluation of a study by Van Horn et al. (Ref. 69).

FDA stands by its evaluation of the Van Horn study. FDA criticized the study because there are significant changes in diet between the control and test group in total fat intake, saturated fat intake, and monounsaturated fat intake, and the authors did not demonstrate that these changes did not contribute to the cholesterol-lowering effect observed.

51. Another comment suggested that weight loss is not a confounder, but rather a result of fibers, ability to effect weight reductions independently of changes in caloric or fat intake.

FDA disagrees with this comment. Although this may be a possible mechanism of action, no studies reviewed have provided clear evidence of this.

52. One comment stated that confounding variables and lack of a mechanism of action are not a valid basis for denying a link between ingestion of fiber and reduced, risk of heart disease which experimental evidence shows in fact exists.

FDA disagrees with the comment's description of the basis for its proposed action. If factors such as weight loss, changes in diet, lifestyle changes, and/or exercise, which are known to influence serum cholesterol, are not controlled in a clinical study, or if analytical methods for determining the soluble fiber content in food sources are not clearly established, the specificity for an effect of soluble fiber on serum cholesterol cannot be determined. In its proposal, FDA made a tentative decision to deny a health claim regarding dietary fiber and CVD for a number of reasons, including confounding factors identified in many of the clinical studies reviewed, but not because there is no recognized mechanism(s) of action for hypolipidemic effects of different soluble fibers. For a more thorough discussion of FDA's proposal to deny a health claim on dietary fiber and CVD in the proposed rule, see 56 FR 60582 at 60591 through 60592. FDA believes that, for health claims to be educational and result in changed eating habits, the claims should be truthful and not misleading.

H. Conclusions From Comments

FDA agrees with many of the comments that a problem in determining the relationship between dietary fiber and heart disease is the fact that dietary fiber is a diverse group of chemical substances that may be associated with different physiological functions, and that the analytical methodology to identify the soluble fiber content of a food may not be predictive of the likely physiological effect.

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

Overall, the currently available scientific evidence is not sufficiently conclusive or specific for soluble fiber per se to justify use of a health claim relating the intake of dietary soluble fiber to a reduced risk of heart disease. A major limitation in designing and evaluating research studies has been the need for better defined measures of dietary soluble fiber and standardized descriptions for source, type, and amount of dietary soluble fiber. Commonly used analytical methodologies do not detect many of the characteristics that may vary among fibers and that may be related to biological function (e.g., particle size, chemical composition, water-holding capacity). Other components associated with soluble fiber in foods (e.g., tocotrienols) may also have some cholesterol-lowering capabilities. The inability to detect many of the differences among fibers, fiber components, and other substances in foods which contain soluble fiber, and the general lack of conclusions as to the mechanism(s) of action of soluble fibers raise questions about the ability of commonly used analytical measures of dietary fiber to adequately predict biological actions of specific fibers. For these reasons, FDA is not authorizing use of a health claim relating dietary fiber to a decreased risk of CHD.

FDA's decision is consistent with recent conclusions reached about the state of the scientific evidence by the National Heart, Lung, and Blood Institute of the National Institutes of Health (Ref. 155) and recommendations in the Institute of Medicines report "Nutrition Labeling: Issues and Directions for the 1990s" (Ref. 81). 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, heart disease, and diabetes mellitus 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. 48 and 81). 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 (particularly soluble fiber) and a reduction in the risk of heart disease. In reaching this decision, the agency considered all comments received in response to its proposed rule (56 FR 60582), 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 Saturated Fat and Cholesterol and High in Fruits, Vegetables, and Grain Products, Foods That Contain Fiber, Particularly Soluble Fiber, to a Reduced Risk of CHD

FDA has reviewed the numerous authoritative documents, including Federal government reports, as well as recent research on dietary fiber and CHD 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 saturated fat and cholesterol and high in fruits, vegetables, and grain products, foods that are low in saturated fat and cholesterol and are good sources of dietary fiber, to reduced risk of heart disease.

FDA agrees with the comments that show that dietary patterns that are low in saturated fat and cholesterol and high in fruits, vegetables (including legumes), and grain products are associated with a decreased risk of CHD. Although the specific roles of the numerous potentially protective substances in such plant foods are not yet understood, populations with diets rich in these foods experience many health advantages, including lower rates of heart disease. Currently, there is not scientific agreement as to whether the observed protective effects against heart disease are due to a combination of nutrient components of the foods, including soluble fiber, to other components of soluble fiber-rich diets (for example, potassium and magnesium), to displacement of saturated fat and cholesterol from the diet, or to non-nutritive substances in these foods.

Thus, the conclusion that diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products, foods low in saturated fat and cholesterol and containing soluble fiber, are associated with a reduced risk of heart disease is consistent with the available scientific evidence. The fact that these foods contain dietary fiber, particularly soluble fiber, can serve, therefore, as a useful marker for identifying those fruits, vegetables, and grain products which, when added to diets low in saturated fat and cholesterol may help in reducing blood LDL-cholesterol levels. 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 (a substance) in a statement about the value of fruit, vegetables, and grain products in reducing the risk of heart disease. Thus, the health claim permitted under this regulation to be used on labels and labeling of certain foods associates diets low in saturated fat and cholesterol and high in vegetables, fruit, and grain products, that contain soluble fiber with a reduced risk of heart disease.

VI. Rationale and Description of the Final Regulation

A. Relationship and Significance Statements

In new § 101.77(a), the summary of the relationship between diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain soluble fiber and reduced heart disease risk is consistent with the conclusions reached in the review of the scientific evidence. Although the specific roles of dietary soluble fiber, or of specific soluble fibers and 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 soluble-fiber-containing foods are associated with lower blood LDL-cholesterol levels and with reduced risk of heart disease. These diets are generally low in saturated fat, cholesterol and total fat, nutrients known to have a detrimental effect on blood LDL-cholesterol levels, and therefore, on risk of heart disease. Dietary soluble fiber can be used as a marker to identify the types of foods which correlate with reduced heart disease risk, and whose addition to diets low in saturated fat and cholesterol is considered to be useful in lowering blood LDL-cholesterol (Ref. 66). The relationship statement in § 101.77 (a) also includes other information about heart disease, such as risk factors, as in other authorized health claims.

New § 101.77(b), on the significance of the relationship between consumption of diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain soluble fiber and reduced risk of heart disease, includes the information that U.S. diets tend to be high in saturated fat and cholesterol and low in fiber-containing fruits, vegetables, and grain products. A discussion of current dietary guidelines on recommended servings of fruits, vegetables, and grain products is also provided.

B. Nature of the Claim

In new § 101.77(c)(2)(i), FDA is authorizing a health claim relating diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain soluble fiber to reduced risk of heart disease. In new § 101.77(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 § 101.77(c)(2)(i)(B), the agency, consistent with other authorized claims, is requiring that the claim use the specific terms "heart disease" or "coronary heart disease" to define the type of disease dealt with by this claim. These disease terms reflect terms commonly used in dietary guidance materials, and are also reflective of the scientific evidence which links these dietary factors to heart disease risk via the intermediate mechanism of reducing blood LDL-cholesterol levels, rather than to the broader category of cardiovascular disease.

In new § 101.76(c)(2)(i)(C), the agency is requiring that the claim discuss only those fruits, vegetables, and grain products that contain dietary fiber, rather than all fruits, vegetables, and grain products. Diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, are correlated with reduced heart disease risk. Thus, a claim discussing those fruits, vegetables, and grain products that contain the marker nutrient, but does not attribute a protective effect to soluble fiber, is consistent with current scientific knowledge.

New § 101.77(c)(2)(i)(D) specifies the terms that can be used to describe the fiber component of the fruits, vegetables, and grain products that bear a health claim. Consistent with the state of the scientific evidence, this paragraph permits a choice among a number of terms, but does not allow terms for specific types of fiber to be used, e.g., those connoting the origin of the fiber. The term "soluble fiber" may be used in combination with a more general term for fiber. This permits reference to soluble fiber, which is a useful marker nutrient for foods associated with reduced risk of heart disease. However, the present scientific evidence does not permit a determination of whether it is the soluble fiber or other components in these foods or displacement of fat that provides the protective effect. Given these uncertainties about the specific role of soluble fiber, it would be misleading to place undue emphasis on soluble fiber standing alone.

New § 101.77(c)(2)(i)(F) requires that health claims specify that development of heart disease depends on many factors. This requirement is intended to prevent consumers from being misled that fruits, vegetables, and grain product intake is the only factor connected with heart disease risk.

In new § 101.77(c)(2)(i)(E), 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. New § 101.77(c)(2)(i)(G) is also consistent with other authorized health claims, and prohibits any attribution of degree of risk for heart disease and fiber-containing fruits, vegetables, and grains. These requirements also standardize use of 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 § 101.77(c)(2)(ii)(A) requires that the food bearing the health claim be or contain a fruit, vegetable, or grain product. 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 § 101.77(c)(2)(ii), but contains only a trivial amount of fruit, vegetable, or grain product, 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 saturated fat and cholesterol and heart disease (published elsewhere In this issue of the **Federal Register**), is requiring in new § 101.77(c)(2)(ii)(B) that foods bearing the health claim meet requirements for "low saturated fat," "low cholesterol," and "low total" fat, or alternatively, belong to a class of products that is "low in saturated fat," "low in cholesterol," and "low in total fat." Low saturated fat and cholesterol diets are associated with reduced heart disease risk. Low or negligible total fat is also one of the characterizing features of diets rich in fiber-containing fruits, vegetables, and grain products. Because the effects of saturated fat and cholesterol are not readily separated from the effects of other nutritive components of fruits, vegetables, and grain products, and because the scientific evidence linking diets low in saturated fat and cholesterol to reduced risk of heart disease is strong, saturated fat and cholesterol are specified as qualifying nutrients. Total fat is also specified as a qualifying nutrient because a low content of total fat is characteristic of dietary patterns which relate to lower heart disease risk, and because it facilitates the ability of consumers to achieve diets low in saturated fat and cholesterol. (See final rule on "Dietary Saturated Fat and Cholesterol and Coronary Heart Disease," published elsewhere in this issue of the **Federal Register**).

In new § 101.77(c)(2)(ii)(C) FDA is requiring that fruits, vegetables, and grain products bearing the authorized health claim contain at least 0.6 g of dietary soluble fiber per reference amount commonly consumed. Because soluble fiber is a qualifying nutrient, FDA, in new § 101.77(c)(2)(n)(D), is requiring declaration of soluble fiber content consistent with requirements in § 101.9(c)(6)(i)(A). The qualifying value of 0.6 g of soluble fiber is based on several considerations. First, an expert panel convened by LSRO (Ref. 39) recommended total dietary fiber intakes of 20 to 30 g daily for adults (see final rule on daily reference valves published elsewhere in this issue of the **Federal Register**). It further recommended that approximately 25 percent (or about 6 g) of this be soluble fiber. This level of soluble fiber represents the same ratio of soluble to insoluble fiber normally found in foods and for which there is a long history of use, and therefore was considered by the panel to be safe. Since current U.S. dietary fiber intakes, including soluble fiber intakes, are estimated to be approximately half of the recommended levels, Americans would need to double their intakes to meet the current dietary guidelines. A total daily intake of 6 g of soluble fiber from fruits, vegetables, and grains is consistent with current dietary guidelines for the general population.

The qualifying criterion of 0.6 g per reference amount customarily consumed is also consistent with the definition of a "good source" of a nutrient (i.e., 10 percent of the daily reference value (DRV)) in the final rule on general requirements for nutrient content claims published elsewhere in this issue of the **Federal Register**. Although there is no DRV for soluble fiber, the requirement that a nutrient be present at 10 percent of a reference standard has been set as a qualifying level in other regulations authorizing health claims. (See the final rules on antioxidant vitamins and cancer and on fiber cancer published elsewhere in this issue of the **Federal Register**. The 10 percent level is deemed useful and appropriate because very few foods could naturally meet the requirement for a "high" source of soluble fiber. The current dietary guidance recommendations of five or more servings of fruits and vegetables and six or more servings of grain products daily, if followed, would likely result in intakes of soluble fiber close to or exceeding the recommended daily intake of 6 g. Thus, use of a qualifying criterion consistent with that used to define a "good" source for nutrients which have DRV's provides for an amount that allows a number of fruits, vegetables, and grain products to qualify, and is consistent with current dietary guidelines for general dietary patterns. Without this alternate level, very few fruits, vegetables, and grain products would qualify for the health claim, which would be contrary to the available scientific evidence and to the purpose of health claims.

Section 101.77(c)(2)(ii)(C) also requires that foods qualify as a good source of soluble fiber based on their natural level of soluble fiber. This means that foods which require fortification with soluble 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 intakes of fruits, vegetables, and grains in their native form correlate with reduced heart disease risk. Because there are not sufficient data that specifically identify dietary soluble fiber, or particular components of soluble fiber, as the cause of a reduction in heart: disease risk, and because this nutrient is being used as a marker for the substance or substances in fruits, vegetables, and grain products that provide the observed protective effect, it is the native composition of the foods that identifies their usefulness.

D. Optional Information

Under new § 101.77(d), similarly to other authorized health claims, health claims may identify additional risk factors for heart disease. 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 saturated fat and cholesterol 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. Consistent with other health claim regulations, the claim may also include information on the prevalence of heart disease 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. Finally, because consumers frequently know their cholesterol levels or can determine their levels through readily available facilities in shopping mails and health clinics, the agency, similarly to other authorized health claims, is requiring that when information in the claim allows consumers to "self-diagnose" their own risk level, that additionally, the claim indicate the need for medical guidance if a consumer falls within a risk category.

Similarly to the requirements in § 101.73 on "Dietary Saturated Fat and Cholesterol and Coronary Heart Disease," the claim may indicate that the relationship between diets low in saturated fat and cholesterol and high in fruits, vegetables, and grains that contain fiber, particularly soluble fiber, is through the intermediate link of "blood cholesterol" or "blood total-and LDL-cholesterol." Such information is useful to consumers, but could add unnecessarily to the length and complexity of the required health claim. For these reasons, this provision is optional rather than mandatory.

E. Model Health Claims

In new § 101.77(e), FDA is providing model health claims to illustrate the requirements of new § 101.77. 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 (56 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 food labeling proposals of November 27, 1991 (56 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 in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Abraham, Z. D., and T. Mehta, "Three-week Psyllium Supplementation: Effect on Plasma Cholesterol Concentrations, Fecal Steroid Excretion, and Carbohydrate Absorption in Men," *American Journal of Clinical Nutrition*, 47:67-74,1988.

2. Anderson, J. W., D. A. Deakins, T. L. Floore, B. M. Smith, and S. E. Whitis, "Dietary Fiber and Coronary Heart Disease," in: Clydesdale, F. M., ed., *Critical Reviews in Food Science and Nutrition*, Vol. 29, New York, pp. 95-137, 1990.

3. Andersen, J. W., N. H. Gilinsky, D. A. Deakins, S. F. Smith, D. S. O'Neal, D. W. Dillon, P. R. Oeltgen, "Lipid Responses of Hypercholesterolemic Men to Oat-bran and Wheat bran Intake," *American Journal of Clinical Nutrition*, 54:678-83, 1991.

4. Anderson, J. W., N. J. Gustafson, D. B. Spencer, J. Tietyen, C. A. Bryant, "Serum Lipid Response of Hypercholesterolemic Men to Single and Divided Doses of Canned Beans," *American Journal of Clinical Nutrition*, 51:1013-9, 1990.

5. Anderson, J. W., S. Riddell-Lawrence, T. L. Floore, D. W. Dillon, P. R. Oeltgen, "Effects of Refined Bakery Products on Serum Cholesterol Levels in Hypercholesterolemic Men," unpublished, 1991.

6. Anderson. J. W., D. B. Spencer, C. C. Hamilton, S. F. Smith, J. Tietyen, C. A. Bryant, P. Oeltgen, "Oat-bran Cereal Lowers Serum Total and LDL Cholesterol in Hypercholesterolemic Men," *American Journal of Clinical Nutrition*, 52:495-499, 1990.

7. Andersen, J. W., L. Story, B. Sieling, W. J. L. Chen, M. S. Petro, J. Story, "Hypocholesterolemic Effects of Oat-bran or Bean Intake for Hypercholesterolemic Men," *American Journal of Clinical Nutrition*, 40:1146-55, 1984.

8. Andersen, J. W., N. Zettwoch, T. Feldman, J. Tietyen-CIark, P. Oeltgen, C. W. Bishop, "Cholesterol-lowering Effects of Psyllium Hydrophilic Mucilloid for Hypercholesterolemic Men," *Archives of Internal Medicine*, 148:292-296, 1988.

9. Aro, A., M. Uusitupa, E. Voutilainen, T. Korhonen, "Effects of Guar Gum in Male Subjects With Hypercholes-terolemia," *American Journal of Clinical Nutrition*, 39:911-916, 1984.

10. Beling, S., L. Detrick, W. Castelli, "Serum Cholesterol Response to a Processed Oat Bran Cereal Among Hypercholes-terolemics on a Fat-modified Diet," unpublished clinical trial submitted by the Quaker Oats Co., 1991.

11. Bell. L. P., K. J. Hectorn, Reynolds, H., Balm, T. K., Hunninghake, D. B. "Cholesterol-lowering Effects of Psyllium Hydrophilic Mucilloid—Adjunct Therapy to a Prudent Diet for Patients With Mild to Moderate Hypercholesterolemia," *Journal of the American Medical Association*, 261:3419-3423, 1989.

12. Bell, L. P., K. J. Hectorn, H. Reynolds, D. B. Hunninghake, "Cholesterol-Lowering Effects of Soluble Fiber Cereals as Part of a Prudent Diet for Patients With Mild to Moderate Hypercholesterolemia," *American Journal of Clinical Nutrition*, 52:1020-6, 1990.

13. Burr, M. L., J. F. Gilbert. R. M. Holliday, P. C. Elwood, A. M. Fehily, S. Rogers. P. M. Sweetnam, N. M. Deadman, "'Effects of Changes In Fat, Fish, and Fiber Intakes on Death and Myocardial Reinfarction: Diet and Reinfarction Trial (DART)," *Lancet*, pp. 757-761, September 30, 1989.

14. Consensus Development Panel, "Lowering Blood Cholesterol to Prevent Heart Disease," *Journal of the American Medical Association*, 253:2080-86, 1985.

15. Davidson, M. H., L. D. Dugan, J. H. Bums, J. Bova, K. Story, K. B, Drennan, "The Hypocholesterolemic Effects of Beta-glycan in Oatmeal and Oat Bran—A dose-controlled Study," *Journal of the American Medical Association*, 265(14):1833-39, 1991.

16. Demark-Wahnefried, W., J. Bowering, P. S. Cohen, "Reduced Serum Cholesterol With Dietary Change Using Fat-modified and Oat Bran Supplemented Diets," *Journal of the American Dietetic Association*, 90:223-9, 1990.

17. Furda, I., "Interaction of Dietary Fiber with Lipids—Mechanistic Theories and Their Limitations," in: Furda, I., C. J, Brine, eds., *New Developments in Dietary Fiber*, New York: Plenum Press, p. 67-80,1990.

18. Glassman, M., Spark. A., Berezin, S., Schwarz, S., "Treatment of Type Iia Hyperilpidemia in Childhood by a Simplified American Heart Association Diet and Fiber Supplementation," *American Journal of Diseases of Children*, 144:973-76, 1990.

19. Gold, K. V., D. M. Davidson, "Oat Bran as a Cholesterol-reducing Dietary Adjunct in a Young, Healthy Population," Western Journal of Medicine, 148:299-302, 1988.

20. Grande, F., J. T. Anderson, A. Keys, "Effect of Carbohydrates of Leguminous Seeds, Wheat and Potatoes on Serum Cholesterol Concentration in Man," *Journal of Nutrition*, 86:313-317, 1965.

21. Grande, F., J. T. Anderson, A. Keys, "Sucrose and Various Carbohydrate-Containing Foods and Serum Lipids in Man," *American Journal of Clinical Nutrition*, 27:1043-1051, 1974.

22. Jenkins. D. J. A., A. R. Leeds, C. Newton, J. H. Cummings, "Effect of Pectin, Guar Gum, and Wheat Fiber on Serum Cholesterol," *Lancet*, i:1116-1117, 1975.

23. Jenkins, D. J. A., D. Reynolds, A. R. Leeds, A. L. Waller, J. H. Cummings, "Hypocholesterolemic Action of Dietary Fiber Unrelated to Fecal Bulking Effect," *American Journal of Clinical Nutrition*, 32:2430-2435, 1979.

24. Judd. P. A., A. S. Truswell, "Dietary Fibre and Blood Lipids in Man," in: "Dietary Fiber Perspectives: Reviews and Bibliography," A. R. Leeds, A. Avenell, eds. London: John Libbey and Co., pp. 23-39, 1985.

25. Kahn, R. F., K. W. Davidson, J. Garner, R. S. McCord. "Oat Bran Supplementation for Elevated Serum Cholesterol," *Family Practice Research Journal*, 10:37-46, 1990.

26. Keenan, J. M., J. B. Wenz, S. Myers, C. Ripsin, Z. Huang, "Randomized Controlled Cross-over Trial of Oat Bran in Hypercholes-terolemic Subjects," in Press, 1991.

27. Kesaniemi, Y. A., S. Tarpila, T. A. Miettinen. "Low versus High Dietary Fiber and Serum, Biliary, and Fecal Lipids in Middle aged Men," *American Journal of Clinical Nutrition*, 51:1007-12, 1990.

28. Kestin, M., R. Moss, P. M. Clifton, P. J. Nestel. "Comparative Effects of Three Cereal Brans on Plasma Lipids, Blood Pressure, and Glucose Metabolism in Mildly Hypercholesterolemic Men," *American Journal of Clinical Nutrition*, 52:661-6, 1990.

29. Keys, A., J. T. Anderson, F. Grande, "Diet-type (Fats Constant) and Blood Lipids in Man," *Journal of Nutrition*, 70:257-266, 1960.

30. "Coronary Heart Disease in Seven Countries," Keys, A., Ed., *Circulation*, 41 (Suppl. 1).

31. Khaw, K., E. Barret-Connor, "Dietary Fiber and Reduced Ischemic Heart Disease Mortality Rates in Men and Women: A 12-year Prospective Study," *American Journal of Epidemiology*, 126:1093-1102, 1987.

32. Kirby, R. W., J. W. Anderson, B. Sieling, E. D. Rees, W. J. L. Chen, R. E. Miller, R. M. Kay, "Oat-bran Intake Selectively Lowers Serum Low-density Lipoprotein Cholesterol Concentrations of Hypercholesterolemic Men," *American Journal of Clinical Nutrition*, 34:824-829, 1981.

33. Kris-Etherton, P. M., D. Krummel, M. E. Russell, D. Dreon, S. Mackey, J. Borchers, P. D. Wood, "National Cholesterol Education Program—The Effect of Diet on Plasma Lipids, Lipoproteins, and Coronary Heart Disease." *Journal of the American Dietetic Association*, 88:1373-1400, 1988.

34. Kritchevsky, D., "Lipid Metabolism and Coronary Heart Disease," in: "Dietary Fibre, Fibre-depleted Foods and Disease," Trowell, H., D. Burkitt, K. Heaton, Eds., New York: Academic Press. pp. 305-313, 1985.

35. Lampe, J. W., J. L Slavin, K. S. Baglien, W. O. Thompson, W. C. Duane, J. H. Savoral, "Serum Lipid and Fecal Bile Acid Changes with Cereal, Vegetable, and Sugar-beet Fiber Feeding," *American Journal of Clinical Nutrition*, 53 :1235-1241, 1991.

36. Lanza, E., D. Y. Jones, G. Block, L. Kessler, "Dietary Fiber Intake in the U. S. Population," *American Journal of Clinical Nutrtition*, 46:790-797, 1987.

37. Levin, E. G., V. T. Miller, R. A. Muesiag, D. B. Stoy, T. K. Balm, J. C. LaRosa, "Comparison of Psyllium Hydrophilic Mucilloid and Cellulose as Adjuncts to a Prudent Diet in the Treatment of Mild to Moderate Hypercholesterolemia," *Archives of Internal Medicine*, 150:1822-27.

38."'Nutrition, Lipids, and Coronary Heart Disease: A Global View," Levy, R., B. Rifkind, B. Dennis, N. Ernst, Eds., Raven, New York, 1979.

39. LSRO, FASEB, "Physiological Effects and Health Consequences of Dietary Fiber," Bethesda, MD, 1987.

40. LSRO, FASEB, "Dietary Fiber and Cardiovascular Disease," Bethesda, MD, 1991.

41. Lipids Research Clinics Program, "The Lipid Research Clinics Coronary Primary Prevention Trial Results II," in The Relationship of Reduction in Incidences of Coronary Heart Disease to Cholesterol Lowering, *Journal of the American Medical Association*, 251:365-74, 1984.

42. Little, P., G. Girling, A. Craven, A. Trafford, "The Effect of a Combination Low Sodium, Low Fat, High Fibre Diet on Serum Lipids in Treated Hypertensive Patients," *European Journal of Clinical Nutrition*, 44:293-300, 1990.

43. Lo, G. S., T G. Cole, "Soy Cotyledon Fiber Products Reduce Plasma Lipids" *Atherosclerosis*, 82:59-67, 1990.

44. Mcintosh, G. H., J. Whyte, R. McArthur, P. J. Nestel, "Barley and Wheat Foods: Influence on Plasma Cholesterol Concentrations in Hypercholesterolemic Men," *American Journal of Clinical Nutrition*, 53:1205-1209, 1991.

45. Mclvor., M. E., C. C. Cummings, A. I. Mendeloff, "Long-term Ingestion of Guar Gum is Not Toxic in Patients with Noninsulin-Dependent Diabetes Mellitus," *American Journal of Clinical Nutrition*, 41:891-894, 1985.

46. Minister of National Health and Welfare Canada, *Report of the Expert Advisory Committee Dietary Fibre,* Canadian Government Publishing Centre, Ottawa, Canada, 1985.

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

48. National Research Council/National Academy of Sciences (NAS), "Diet and Health: Implications for Reducing Chronic Disease Risk," National Academy Press: Washington, DC, 1989.

49. National Research Council (NRC). "Recommended Dietary Allowances," 10th Edition, National Academy Press: Washington, DC, 1989.

50. Newman, R. K., S. E. Lewis, C. W. Newman R. J. Boik, R. T. Ramage, "Hypocholesterolemic Effect of Barley Foods on Healthy Men," *Nutritional Reports International*, 39:749-769. 1989.

51. Nishina, P. M., R. A Freedland, "Effects of Propionate on Lipid Biosynthesis in Isolated Rat Hepatocytes" *Journal of Nutrition*, 120:668-673, 1990.

52. Ross, R., "Atherosclerosis'" in: Cecil Textbook of Medicince, J. B. Wyngaarden, L. H. Smith, eds., W. B. Saunders Co., Philadelphia, PA, pp. 319-320, 1988.

53. Shutler, S. M., G. M. Bircher, J. A. Tredger. L. M. Morgan, A. F. Walker, A. G. Low, "The Effect of Daily Baked Bean (Phaseolus Vulgaris) Consumption on the Plasma Lipid Levels of Young, Normo-cholesterolaemic Men," *British Journal of Nutrition*, 61:257-65, 1989.

54. Stamler, J., "Nutrition-related Risk Factors For The Atherosclerotic Diseases-Present Status," Progress in Biochemical Pharmacology 19:245-308, 1983.

55. Stewart, R. B., W. E., Hale, M. T. Moore, F. E. Nay, R. G. Marks, "Effect of Psyllium Hydrophilic Mucilliod on Serum Cholesterol in the Elderly" *Digestive Disease and Sciences*, 36:329-334, 1991.

56. Superko, H. R., W. L. Haskell, L. Sawrey-Kubicek, J. W. Farquhar, "Effects of Solid and Liquid Guar Gum on Plasma Cholesterol and Triglyceride Concentrations in Moderate Hypercholesterolemia," *American Journal of Cardiology*, 62:51-55, 1988.

57. Swain. J. F., I. L. Rouse, C. B. Curley, F. M. Sacks, "Comparison of the Effects of Oat Bran and Low fiber Wheat on Serum Lipoprotein Levels and Blood Pressure" *New England Journal of Medicine*, 322:147-52, 1990.

58. Taneja, A., C. M. Bhat, A. Arora, A. P. Kaur, 1989. "Effect of Incorporation of Isabgol Husk in a Low Fibre Diet on Faecal Excretion and Serum Levels of Lipids in Adolescent Girls," *European Journal of Clinical Nutrition*, 43:197-202, 1989.

59. Tuomilehto, J., M., Silvasti, A. Aro, P. Karttunen, C. Gref, C. Ehnholm, M. Uusitupa "Long Term Treatment of Severe Hvpercholesterolaemia With Guar Gum," *Atherosclerosis*, 72:157-162, 1988.

60. Tuomilehto, J., E. Voutilainin, J. Huttuenen, S. Vinni, K. Homan, "Effect of Guar Gum on Body Weight and Serum Lipids in HypercholesteroIemic Females," *Acta Medica Scandinavian*, 208:45-48, 1980.

61. I. H. Ullrich, "Evaluation of a High-fiber Diet in Hvperlipidemia: A Review," Journal of the American College of Nutrition, 6(1):19-25, 1987.

62. USDA and DHHS, "Nutrition and Your Health: Dietary Guideline for Americans" 3rd Ed., Home and Garden Bulletin No. 232, U.S. Government Printing Office, Washington, DC.

63. DHHS, Public Health Service (PHS), "The Surgeon General's Report on Nutrition and Health," U.S. Government Printing Office, Washington, DC, 1988.

64. DHHS, PHS, "Healthy People 2000: National Health Promotion and Disease Prevention Objectives," Washington, DC, 1990.

65. DHHS, PHS and the National Institutes of Health (NIH), "National Cholesterol Education Program: Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," NIH, Bethesda, MD, 1989.

66. DHHS, PHS and the National Institutes of Health, "National Cholesterol Education Program: Population Panel Report," Bethesda, MD, 1989.

67. Van Horn. L., C. Ballew, K. Liu, K. Ruth, A. McDonald. J. E. Hilner, G. L. Burke, P. J. Savage, C. Bragg, B. Caan, D. Jacobs, M. Slattery, S. Sidney, "Diet, Body Size, and Plasma Lipids-lipoproteins in Young Adults: Differences by Race and Sex," *American Journal of Epidemiology*, 133:9-22, 1991.

68. Van Horn, L., Emidy, L. A., Liu, K., Liu, Y., Ballew, C., King. J., Stamler, J. 1988, Serum "Lipid Response to a Fat-modified, Oatmeal -enhanced Diet," *Preventive Medicine*, 17:377-386.

69. Van Horn, L., A. Moag-Stahlberg, K. Liu, C. Ballew, K. Ruth, R. Hughes, J. Stamler, "Effects on Serum Lipids of Adding Instant Oats to Usual American Diets," *American Journal of Public Health*, 81:183-88, 1991.

70. Venter, C. S., H. H. Vorster, D. G. Van der Nest, "Comparison Between Physiological Effects of Konjac-glucomannan and Propionate in Baboons Fed Westem Diets," *Journal of Nutrition*, 120:1046-1053, 1991.

71. World Health Organization, "Diet, Nutrition, and the Prevention of Chronic Diseases," WHO, Geneva, Switzerland, 1990.

72. Nishina, P. M., R. A. Freedland, "Effects of Propionate on Lipid Biosynthesis in Isolated Rat Hepatocytes," *Journal of Nutrition*, 120:668-673, 1990.

73. Story, J. A., "'Modification of Steroid Excretion in Response to Dietary Fiber: Basic and Clinical Aspects," Vahouny, G. V., D., Kritchevsky. Eds., New York: Plenum Press, pp. 253-264.

74. Sugano, M., I. Ikeda, K. Imaizumi, Y. Lu, "Dietary Fiber—Chemistry, Physiology, and Health Effects," Kritchevsky, D., Bonfield, C., Anderson, J. W., eds., New York: Plenum Press, p. 137-156, 1990.

75. Vahouny. G. V., M. M. Cassidy, "Dietary Fibers and Absorption of Nutrients," *Proceeding of the Society for Experimental Biology and Medicine*, 180:432-446, 1985.

76. National Cancer Institute, "Cancer Prevention: Good News, Better News, Best News," NIH Publ. No. 84-2671, National Institutes of Health (NIH), Public Health Service (PHS), Department of Health and Human Services (DHHS), U.S. Government Printing Office, Washington, DC, 1984.

77. National Cancer Institute, "Diet, Nutrition & Cancer Prevention: to Food Choices," NIH Publ. No. 87-2878, NIH, PHS, DHHS, U.S. Government Printing Office, Washington, DC, 1987.

78. National Cancer Institute, "Eat More Fruits and Vegetables* * * Five a Day for Better Health," NIH Pub. No. 92-3248, NIH, PHS, DHHS, U.S. Government Printing Office, Washington, DC, 1991.

79. Carroll, M., C. Sempos, R. Briefel, et al., "Serum Lipids of Adults 20-74 years, United States, 1976-80," Vita! Health Statistics II, U.S. DHHS, HHS, National Center for Health Statistics, in press, 1992.

80. DHHS, PHS and NIH, NCEP, "Eating to Lower Your High Blood Cholesterol," NIH, Bethesda, MD, 1989.
81. Institute of Medicine, National Academy of Sciences, "Nutrition Labeling* * * Issues and Directions for the 1990s," National Academy Press, Washington, DC, 1990.
82. Burr. M. L., "Vegetarianism, Dietary Fiber, and Mortality," *American Journal of Nutrition*, 36:873-877,1982.
83. Leadbetter. J., M. J. Ball, J. I. Mann, "Effects of Increasing Quantities of Oat Bran in Hypercholesterolemic People," *American Journal of Clinical Nutrition*, 54:841-845, 1991.
84. Cara. L., P. Borel, M. Armand, M. Senft, H. Lafont, et al., "Plasma Lipid Lowering Effects of Wheat Germ in Hypercholesterolemic Subjects," *Plant Foods for Human Nutrition*, 41:135-150, 1991.
85. Karlander, S., I. Armyr, S. Efendic, "Metabolic Effects and Clinical Value of Beet Fiber Treatment in NIDDM Patients," *Diabetes Research and Clinical Practice,* 11:65-72, 1991.
86. Israelsson, B., G. Jarnblad, K. Persson, "Serum Cholesterol Reduced with Fibrex, a Sugar-beet Fiber Preparation," unpublished, submitted with comments from the food industry, 1991.
87. Spiller. G, A., J. W. Farquhar, J. E. Gates, S. F. Nichols, "Guar Gum and Plasma Cholesterol, Effect of Guar Gum and an Oat Fiber Source on Plasma Lipoproteins and Cholesterol in Hypercholesterolemic Adults," *Arteriosclerosis and Thrombosis*, 11:1204-1208, 1991.
88. Kawatra, A., A. C. Kapoor. S. Seghal, "Hypocholesterolemic Effect of Guar Gum in Overweight Adults." *Plant Foods for Human Nutrition*, 41:241-245, 1991.
89. Tinker, L. F., B. O'Schneeman, P. A. Davis, D. D. Gallaher, C. R. Waggoner, "Consumption of Prunes as a Source of Dietary Fiber in Men with Mild Hypercholesterolemia," *American Journal of Clinical Nutrition*, 53:1259-1265, 1991.
90. Earll, J. M., "Feasibility and Metabolic Effects of a Precisely Measurable Dietary Food Supplement," unpublished report submitted with comments, 1986.
91. Bremer. J. M., R. S. Scott, C. J. Lintott, "Oat Bran and Cholesterol Reduction: Evidence Against Specific Effect," *Australia and New Zealand Journal of Medicine,* 21:422-426, 1991.
92. Anderson, J. W., T. L. Floore, P. B. Geil, D. S. O'NeaL T. K. Balm, "Hypocholesterolemic Effects of Different Bulk-forming Hydrophilic Fibers as Adjuncts to Dietary Therapy in Mild to Moderate Hypercholesterolemia," *Archives of Internal Medicine*, 151:1597-1602, 1991.
93. Jenkins, D. J. A., S. Mueller, T. M. S. Wolever, V. Rao, T. Ransom, D. Boctor, et al. "High Soluble Fiber Foods Reduce Serum Lipids Even When Diets are Already Low in Saturated Fat and Cholesterol," unpublished report submitted from industry, 1991.
94. Jenkins, D J. A., T. M. S. Wolever, V. Rao, R. Hegele, S. Mitchell, et al., "High Fiber Foods Reduce Serum Lipids Even on Diets Low in Saturated Fat and Cholesterol," unpublished report from industry, 1991.
95. Anderson, J. W., "Cholesterol-lowering Effects of Psyllium-enriched Cereal," unpublished report from industry, 1991.
96. Resnicow, K., J. Barone, A. Engle, S. Miller, N. Haley, et al., "Diet and Serum Lipids in Vegan Vegetarians: A Model for Risk Reduction," *Journal of the American Dietetic Association*, 91:447-453, 1991.
97. Kirsten, R., B. Domning, K. Nelson, K. Nemeth, G. Oremek, et al., "Influence of Guar on Serum Lipids in Patients with Hyperlipidaemia," *European Journal of Clinical Pharmacology*, 37:117-120, 1989.
98. Neal. G. W., T. K. Balm, "Synergistic Effects of PsyIlium in the Dietary Treatment of Hypercholesterolemia," *Southern Medical Journal*, 83:1131-1137, 1990.
99. Niemi. M. K., S. M. Keinanen-Kiukaanniemi, P. I. Salmela, "Long-term Effects of Guar Gum and Microcrystalline Cellulose on Glycaemic Control and Serum Lipids in Type 2 Diabetes," *European Journal of Clinical Pharmacology*, 34:427-429, 1988.
100. Uusitupa, M., 0. Siitonen, K. Savolainen, M. Silvasti, I. Penttila, M. Parviainen, "Metabolic and Nutritional Effects of Long-term Use of Guar Gum in the Treatment of Noninsulin-dependent Diabetes of Poor Metabolic Control," *American Journal of Clinical Nutrition*, 49:345-351, 1989.
101. Wolever, T., D. J. A. Jenkins, S. Mueller, C. Mehling, L. Katzman, et al., "Psyllium Reduces Blood Lipids to a Similar Extent in Hyperlipidemic Men and Women," unpublished study submitted with comments.
102. Wolever, T., D. J. A. Jenkins, S. Mueller, D. Boctor, T. P. P. Ransom, et al., "Method of Administration Influences the Serum Cholesterol-lowering Effect of Psyllium," unpublished study submitted with comments.
103. O'Connor, R. R., J. Jin, D. S. Hwang, "A Multicenter Study of a Five Fiber Supplement in the Treatment of Hypercholesterolemia." final report, unpublished study submitted with comments, 1992.
104. Whyte, J., R. McArthur, D. Topping, P. Nestel, "Oat Bran Lowers Plasma Cholesterol in Mildly Hypercholesterolemic Men," *Journal of the American Dietetic Association*, 92:446-449, 1992.
105. Cerda, J. J., F. L. Robbins, C. W. Burgin, T. G. Baumgartner, R.W. Rice, "The Effects of Grapefruit Pectin on Patients at Risk for Coronary Heart Disease Without Altering Diet or Lifestyle," *Clinical Cardiology*, 11:589-594, 1988.
106. Haskell, W. L., G. A. Spiller, C. D. Jensen, B. K. Ellis, J. E. Gates, "Role of Water-Soluble Dietary Fiber in the Management of Elevated Plasma Cholesterol in Healthy Subjects," *The American Journal of Cardiology*, 69:433-439, 1992.
107. Nervi, F., C. Covarrubias, P. Bravo, N. Velasco, N. Ulloa, et al., "Influence of Legume Intake on Biliary Lipids and Cholesterol Saturation in Young Chilean Men," *Journal of Clinical Nutrition and Gastroenterology*, 96:825-830, 1989.
108. Unpublished study submitted from food industry with comments. "Cholesterol-lowering Effects of Ready-to-eat Cereal Containing Psyllium," 1991.
109. Spencer, K. M., D. L. Gee, "The Cholesterol Lowering Effect of a Fiber Supplemented Apple Juice Beverage in Men with Mild Hypercholesterolemia," unpublished study submitted with comments from food industry, 1991.
110. Anderson, J. W., L. Story, B Sieling, W. L. Chen, "Hypocholesterolemic Effects of High Fibre Diets Rich in Water-soluble Plant Fibres," *Journal of the Canadian Dietetic Association,* vol. 45, No. 2, 1984.
111. Tumbull, W. H., A. R. Leeds, "Reduction of Total and LDL-cholesterol in Plasma by Rolled Oats." *Journal of Clinical Nutrition and Gastroenterology*, 2:1-4, 1987.
112. Crane, N., memo to file, Clinical Nutrition Branch, October 15, 1992.
113. Anderson, J. W., N. H. Gilinsky, D. A. Deakins, S. F. Smith, D. S. O'Neal, D. W. Dillon, P. R. Oeltgen, "Lipid Responses of Hypercholesterolemic Men to Oat-bran and Wheat bran Intake." *American Journal of Clinical Nutrition*, 54:678-683, 1991.
114. Fukagawa, N. K., J. W. Anderson, G. Hageman, V. R. Young, K. L. Minaker, "High-carbohydrate, High-fiber Diets Increase Peripheral Insulin Sensitivity in Healthy Young and Old Adults," *American Journal of Clinical Nutrition*, 52:524-528, 1990.
115. Reference letter from Kellogg Co. to FDA, December 5, 1990.
116. Reference letter from FDA to Kellogg Co., December 12, 1990.
117. Walsh. D. E., V. Yaghoubian, A. Behforooz, "Effect of Glucomannan on Obese Patients: A Clinical Study." *International Journal of Obesity*, 8:289-293, 1983.
118. Anderson, J. W., S. Riddell-Mason, N. J. Gustafson, et al., "Cholesterol-lowering Effects of Psyllium-enriched Cereal as an Adjunct to a Prudent Diet in the Treatment of Mild to Moderate Hypercholesterolemia," *American Journal of Clinical Nutrition,* 56:93-98, 1992.
119. Braaten, J. T., M. K. L. Braaten, P. Cradley-White, et al., "Cholesterol Lowering Effect of Oat Gum in Hypercholesterolemic Subjects," unpublished study, 1992.
120. Bridges, S. R., J. W. Anderson, D. A. Deakins et al., "Oat Bran Increases Serum Acetate of Hypercholesterolemic Men." *American Journal of Clinical Nutrition,* 56:455-459.
121. Kashtan, H. H., S. Stern, D. J. A. Jenkins, et al., "Wheat bran and Oat-bran Supplements' Effects on Blood Lipids and Lipoproteins," *American Journal of Clinical Nutrition*, 55:976-980, 1992.
122. Ranhotra, G. S., J. A. Gelroth, R. D. Reeves, et al., "Short-term Lipidemic Responses in Otherwise Healthy Hypercholesterolemic Men Consuming Foods High in Soluble Fiber," *Cereal Chemistry*, 66:94-97, 1989.
123. Zhang, J. G. Hallmans, H. Andersson, et al., "Effect of Oat Bran on Plasma Cholesterol and Bile Acid Excretion in Nine Subjects with Ileostomies." *American Journal of Clinical Nutrition*, 56:99-105, 1992.
124. Marlett, J. A., K. B. Hosig, N. W. Vollendorf, et al., "Mechanism or Serum Cholesterol Reduction by Oat Bran," unpublished study submitted with comments, 1992.
125. Ripsin, C. M., J. M. Keenan, D. R. Jacobs, et al., "Oat Products and Lipid

Lowering—A Meta-analysis," *Journal of the American Medical Association*, 267:3317-3325, 1992.

126. Turnbull, W. H., A. R. Leeds, "The Effect of Rolled Oats and a Reduced/Modified Fat Diet on Apolipoprotein AI and B," *Journal of Clinical and Nutritional Gastroenterology*, 1:15-19, 1989.

127. Ney, D. M., J. B. Lasekan, F. L. Shinnick, "Soluble Oat Fiber Tends to Normalize Lipoprotein Composition in Cholesterol-fed Rats," Journal of Nutrition, 118:1455-1462, 1988.

128. Nishina, P. M., B. O. Schneeman, R. A. Freedland, "Effects of Dietary Fibers on Nonfastin Plasma Lipoprotein and Apolipoprotein Levels in Rats," *Journal of Nutrition*, 121:431-437, 1991.

129. Prentice. N., A. A. Qureshi, W. C. Burger, C. E. Elson, "Response of Hepatic Cholesterol, Fatty Acid Synthesis and Activities of Related Enzymes to Rolled Barley and Oats in Chickens," *Nutrition Reports International*, 26:597-604, 1982.

130. O'Mahony, S., "Biofunctional Properties of Oat-cereal Fractions. No. 7," unpublished studies submitted with comments, 1975.

13L Qureshi, A. A., W. C. Burger, K. Prentice, et al., "Regulation of Lipid Metabolism in Chicken Liver by Dietary Cereals," *Journal of Nutrition*, 110:388-393, 1980.

132. Ranhorta, G. S., J. A. Gelroth, K. Astroth, C. S. Rao, "Relative Lipidemic Responses in Rats Fed Oat Bran or Oat Bran Concentrate," *Cereal Chemistry*, 67:509-511, 1990.

133. Shinnick, F. L., M. J. Longacre, S. L. Ink, J. A. Marlett, "Oat Fiber: Composition Versus Physiological Function in Rats," *Journal of Nutrition*, 118:144-151, 1988.

134. Shinnick, F, L., S. L. Ink, J. A. Marlett, "Dose-Response to a Dietary Oat Bran Fraction in Cholesterol-Fed Rats," *Journal of Nutrition*, 120:561-568, 1990.

135. Rogel, A. M., P. Vohra, "Alteration of Lipid Metabolism in Japanese Quail by Feeding Oat Hulls and Brans," *Poultry Science*, 62:1045-1053, 1983.

136. O'Mahony, S., "Biofunctional Properties of Oat-cereal Fractions. No. 18," unpublished studies submitted with comments, 1976.

137. Bengtsson, S., P. Aman, H. Graham, et al., "Chemical Studies on Mixed-Linked β-Giucans in Hull-less Barley Cultivars Giving Different Hypocholesterolemic Responses in Chickens," *Journal of Science and Food Agriculture*, 52:435-445, 1990.

138. Kritchevsky. D., S. A. Tepper, G. T. Goodman, et al., "Influence of Oat and Wheat Bran on Choleslerolemia in Rats," *Nutrition Reports International*, 29:1353-1359, 1984.

139. Klopfenstein, C. F., R. C. Hoseney, "Cholesterol Lowering Effect of Beta-Glucan-Enriched Bread," *Nutrition Reports International*, 36:1091-1098, 1987.

140. Kahlon, T. S., R. M. Saunders, F. I. Chow, et al., "Influence of Rice Bran, Oat Bran, and Wheat Bran on Cholesterol and Triglycerides in Hamsters," *Cereal Chemistry*, 67:439-443, 1990.

141. Jennings, C. D., K. Boleyn, S. R. Bridges, et al., "A Comparison of the Lipid-Lowering and Intestinal Morphological Effects of Cholestyramine, Chitosan, and Oat Gum in Rats (42773)," *Proceedings of the Society for Experimental Biology and Medicine*, 189:13-20, 1988.

142. Forsythe, W. A., W. L. Chenoweth, M. R. Bennink, "Laxation and Serum Cholesterol in Rats Fed Plant Fibers," *Journal of Food Science*, 43:1470-1472, 1978.

143. Chen, W. L., J. W. Anderson, M. R. Gould, "Effects of Oat Bran, Oat Gum and Pectin on Lipid Metabolism of Cholesterol-fed Rats." *Nutrition Reports International*, 24:1093-1098, 1981.

144. Chen, W. L., J. W. Anderson, "Effects of Plant Fiber in Decreasing Plasma Total Cholesterol and Increasing High-Density Lipoprotein Cholesterol (40671)," *Proceedings of the Society for Experimental Biology and Medicine*, 162:310-313, 1979.

145. Fadel, J. G., R. K. Newman, C. W. Newman, et al., "Hypocholesterolemic Effects of Beta-Glucans in Different Barley Diets Fed to Broiler Chicks," *Nutrition Reports International*, 35:1049-1058, 1987.

146. Chen, W. L., J. W. Anderson, "Effects of Guar Gum and Wheat Bran on Lipid Metabolism of Rats," *Journal of Nutrition*, 109:1028-1034, 1979.

147. Turley, S. D., B. P. Daggy, J. M. Dietschy, "Cholesterol-lowering Action of Psyllium Mucilloid in the Hamster: Sites and Possible Mechanisms of Action," *Metabolism*, 40:1063-1073, 1991.

148. Wilson, J. N., S. P. Wilson, R. P. Eaton, "Dietary Fiber and Lipoprotein Metabolism in the Genetically Obese Zucker Rat," *Arteriosclerosis*, 4:147-153, 1984.

149. Welch, R. W., E. M. Peterson, B. Schramka, "Hypocholesterolemic and Gastrointestinal Effects of Oat Bran Fractions in Chicks," *Nutrition Reports International*, 38:551-561, 1988.

150. Hundemer, J. K., S. P. Nabar, B. J. Shriver, L. P. Forman, "Dietary Sources Lower Blood Cholesterol in C57BL/6 Mice," *Journal of Nutrition*, 121:1360-65, 1991.

151. Ginker, E., F. J. Kubec, J. Vozar, P. Bobek, "Natural Hypocholesterolemic Agent: Pectin Plus Ascorbic Acid," *International Journal of Vitamin Research*, 49:406-412, 1979.

152. Kakis, G., E. Chao, M. Schmidt, et al., "Psyllium Induced Cholesterol Lowering in the Hamster," unpublished study submitted with comments, 1992.

153. LSRO, FASEB, "Evaluation of the Health Aspects of Oat Gum, Okra Gum, Quince Gum, and Psyllium Husk Gum as Food Ingredients," Bethesda, MD, 1982.

154. Schrijver, R. D., D. Fremaut, A. Verheyen, "Cholesterol-lowering Effects and Utilization of Protein, Lipid, Fiber and Energy in Rats Fed Unprocessed and Baked Oat Bran." *Journal of Nutrition*, 122:1318-1324, 1992.

155. Lenfant, C., Letter to David Kessler, October 29, 1992.

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. New § 101.71 is added to subpart E to read as follows:

§ 101.71 Health claims: claims not authorized.

* * * * *

(b) Dietary fiber and cardiovascular disease.

3. New § 101.77 is added to subpart E to read as follows:

§ 101.77 Health claims: fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease.

(a) *Relationship between diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease* (1) Cardiovascular disease means diseases of the heart and circulatory system. Coronary heart disease is the most common and serious form of cardiovascular disease and refers to diseases of the heart muscle and supporting blood vessels. High blood total- and low density lipoprotein (LDL)- cholesterol levels are major modifiable risk factors in the development of coronary heart disease. High coronary heart disease rates occur among people with high blood cholesterol levels of 240 milligrams per deciliter (mg/dL) (6.21 (mmol/L)) or above and LDL-cholesterol levels of 163 mg/dL (4.13 mmol/L) or above. Borderline high risk blood cholesterol levels range from 200 to 239 mg/dL (5.17 to 6.18 mmol/L) and 130 to 159 mg/dL (3.36 to 4.11 mmol/L) of LDL-cholesterol. Dietary lipids (fats) include fatty acids and cholesterol. Total fat, commonly referred to as fat, is composed of saturated fat (fatty acids containing no double bonds), and monounsaturated and polyunsaturated fat (fatty acids containing one or more double bonds).

(2) The scientific evidence establishes that diets high in saturated fat and cholesterol are associated with increased levels of blood total- and LDL-cholesterol and, thus, with increased risk of coronary heart disease. Diets low in saturated fat and cholesterol are associated with decreased levels of blood total- and LDL-cholesterol, and thus, with decreased risk of developing coronary heart disease.

(3) Populations with relatively low blood cholesterol levels tend to have dietary patterns that are not only low in total fat, especially saturated fat and cholesterol, but are also relatively high in fruits, vegetables, and grain products. Although the specific roles of these plant foods are not yet fully understood, many studies have shown that diets high in plant foods are associated with reduced risk of coronary heart disease. These studies correlate diets rich in fruits, vegetables, and grain products and nutrients from these diets, such as some types of fiber, with reduced coronary heart disease risk. Persons consuming these diets frequently have high intakes of dietary fiber, particularly soluble fibers. Currently, there is not scientific agreement as to whether a particular type of soluble fiber is beneficial, or whether the observed protective effects of fruits, vegetables, and grain products against heart disease are due to other components, or a combination of components, in these diets, including, but not necessarily limited to, some types of soluble fiber, other fiber components, other characteristics of the complex carbohydrate content of these foods, other nutrients in these foods, or displacement of saturated fat and cholesterol from the diet.

(b) *Significance of the relationship between diets low in saturated fat and cholesterol, and high in fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease.* (1) Coronary heart disease is a major public health concern in the United States, primarily because it accounts for more deaths than any other disease or group of diseases. Early management of risk factors for coronary heart disease is a major public health goal that can assist in reducing risk of coronary heart disease. There is a continuum of mortality risk from coronary heart disease that increases with increasing levels of blood LDL-cholesterol. Individuals with high blood LDL-cholesterol are at greatest risk. A larger number of individuals with more moderately elevated cholesterol also have increased risk of coronary events; such individuals comprise a substantial proportion of the adult U.S. population. The scientific evidence indicates that reducing saturated fat and cholesterol intakes lowers blood LDL-cholesterol and risk of heart disease in most individuals, including persons with blood cholesterol levels in the normal range. Additionally, consuming diets high in fruits, vegetables, and grain products, foods that contain soluble fiber, may be a useful adjunct to a low saturated fat and low cholesterol diet.

(2) Other risk factors for coronary heart disease include a family history of heart disease, high blood pressure, diabetes, cigarette smoking, obesity (body weight 30 percent greater than ideal body weight), and lack of regular physical exercise.

(3) Intakes of saturated fat exceed recommended levels in many people in the United States. Intakes of cholesterol are, on average, at or above recommended levels. Intakes of fiber-containing fruits, vegetables, and grain products are about half of recommended intake levels. One of the major public health recommendations relative to coronary heart disease risk is to consume less than 10 percent of calories from saturated fat, and an average of 30 percent or less of total calories from all fat. Recommended daily cholesterol intakes are 300 mg or less per day. Recommended total dietary fiber intakes are about 25 grams (g) daily, of which about 25 percent (about 6 g) should be soluble fiber.

(4) Current dietary guidance recommendations encourage decreased consumption of dietary fat, especially saturated fat and cholesterol, and increased consumption of fiber-rich foods to help lower blood LDL-cholesterol levels. Results of numerous studies have shown that fiber-containing fruits, vegetables, and grain products can help lower blood LDL-cholesterol.

(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 saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, with reduced risk of heart disease 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 saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber "may" or "might" reduce the risk of heart disease;

(B) In specifying the disease, the claim uses the following terms: "heart disease" or "coronary heart disease;"

(C) The claim is limited to those fruits, vegetables, and grains that contain fiber;

(D) In Specifying the dietary fiber, the claim uses the term "fiber," "dietary fiber," "some types of dietary fiber," "some dietary fibers," or "some fibers;" the term "soluble fiber" may be used in addition to these terms;

(E) In specifying the fat component. the claims uses the terms "saturated fat" and "cholesterol;" and

(F) The claim indicates that development of heart disease depends on many factors; and

(G) The claim does not attribute any degree of risk reduction for coronary heart disease to diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber.

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

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

(C) The food contains, without fortification, at least 0.6 g of soluble fiber per reference amount customarily consumed;

(D) The content of soluble fiber shall be declared in the nutrition information panel, consistent with §101.9(c)(6)(i)(A).

(d) *Optional information.* (1) The claim may identify one or more of the following risk factors for heart disease about which there is general scientific agreement; A family history of coronary heart disease, elevated blood-, total- and LDL-cholesterol, excess body weight, high blood pressure, cigarette smoking, diabetes, and physical inactivity.

(2) The claim may indicate that the relationship of diets low in saturated fat and cholesterol, and high in fruits, vegetables, and grain products that contain fiber to heart disease is through the intermediate link of "blood cholesterol" or "blood total- and LDL-cholesterol."

(3) The claim may include information from paragraphs (a) and (b) of this section, which summarize the relationship between diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber and coronary heart disease, and the significance of the relationship.

(4) In specifying the nutrients, the claim may include the term "total fat" in addition to the terms "saturated fat" and "cholesterol."

(5) 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 (GPO).

(6) The claim may state that individuals with elevated blood total- and LDL-cholesterol should consult their physicians for medical advice and treatment. If the claim defines high or

normal blood total- and LDL-cholesterol levels, then the claim shall state that individuals with high blood cholesterol should consult their physicians for medical advice and treatment.

(7) The claim may include information on the number of people in the United States who have heart disease. The sources of this information shall be identified, and it shall 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, GPO.

(e) *Model health claims*. The following model health claims may be used in food labeling to characterize the relationship between diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain soluble fiber:

(1) Diets low in saturated fat and cholesterol and rich in fruits, vegetables, and grain products that contain some types of dietary fiber, particularly soluble fiber, may reduce the risk of heart disease, a disease associated with many factors.

(2) Development of heart disease depends on many factors. Eating a diet low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber may lower blood cholesterol levels and reduce your risk of heart disease.

Dated: November 6, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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

BILLING CODE 4160-01-F

Dietary Fiber and Cardiovascular Disease

Study	Study Design	Subjects	Methods	Results	Comments
Anderson et al., 1991 (Ref. 92)	Intervention, parallel, placebo-controlled, randomly assigned to treatment groups after 8 weeks of diet therapy on American Heart Association (AHA) Step 1 diet and stratification by gender and cholesterol level. Purpose of study: to compare hypocholesterolemic effects of two bulk laxatives relative to psyllium and placebo.	163 mild to moderately hypercholesterolemic males and females enrolled in study, 117 completed 8-week diet therapy, and 105 completed the study protocol. Subjects, ages 30 to 70 years, were free living. (total serum cholesterol (TC) 200 to 300 mg/dL and body weight within 130% of ideal.	Subjects consumed AHA Step 1 diet for an 8-week adaptation period followed by an 8-week parallel treatment period. Four doses of test product were taken each day, including one before each meal. Diet monitored with 3-day food records at 4-week intervals. Step 1 diet: Energy from fat—30 to 33%; protein—17 to 18% carbohydrate (CHO)—46 to 51%; Cholesterol--<300 mg/day. Bulk laxative tested: g/day psyllium powder (PSY) 10.2 methylcellulose powder (MC) 6 or 10.2 calcium polycarbophil tablets (CP) 4 cellulose placebo (PSA) 4	Average Diet During Test Period PSY MC CP PLA Energy, Cal 1755 1742 1833 1768 Fat, % of Cal 30 33 32 31 Protein, % Cal 7.6 18 17.5 16.7 CHO, % 49.8 46.1 47.4 50.9 Fiber, g Total 14.5 14.2 13 15.1 Soluble 4.6 4.4 4 4.7 CHOL, mg 225 219 213 190 Baseline Diet phase: TC ↓4.5%; LDL ↓4.7%; HDL ↓2.9%; TG ↓5.8% The difference in TC between the PSY group and the placebo is not significant (↓4.3% difference). Lipids Values—Diet + Fiber Comparison to baseline PSY MC CP PLA TC, % ↓8.2% ↓5.3* ↑2 ↓3.9 LDL, % ↓13.4* ↓7.8* ↑4.1 ↓4.6 HDL, % ↓2.2 ↓4.8* ↑4.8 ↑0.1 LDL/HDL ↓10.8* ↓3.8 ↓1.2 ↓4 TG, % ↑12.4 ↑8.2 ↓10.9* ↓7.3 * Significant from baseline.	No weight change by more than o.5% from baseline. Weights at baseline and final were not given. Compliance reported as good for all test groups.* Side effects reported were mostly gastrointestinal. Choice of cellulose as a placebo is questionable. Cellulose may actually have a cholesterol lowering effect. *No data on saturated fat

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Bremer, J. M. et al., 1991(Ref. 91)	Intervention, randomized, single-blind, cross-over, placebo controlled.	12 hyperlipidemic men and women (TC 220 to 348 mg/dL), free living.	Subjects were stabilized on phase II AHA diet for 3 months prior to study. Base diet: fat 25 to 30% total energy; saturated fat <8%; polyunsaturated fatty acid (PUFA) 5 to 10%; monounsaturated fat >10% cholesterol <250 mg/d; fiber >20 g/1,000 Calories. Two-week run-in with the addition of bread to the diet prior to test. Subjects randomized to oat or wheat group for 4 weeks, followed by 2-week washout, then cross-over to other diet. Bread added to diet in place of other CHO foods. Men consumed 10 to 12 slices bread/day; women consumed 6 slices. Dietary assessment by food records and bread charts. Oat bread / Wheat bread Total fiber, g% 5.2 / 6.1 Insoluble fiber, g% 4.0 / 5.2 Soluble fiber, g% 1.2 / 0.9 Oat bran intake: 34.2 to 68.4 g/day Total dietary fiber intake: Oat period 32.2 g / Wheat period 34.1 g	At beginning of first study period, there was no significant difference between TC, LDL, and HDL between groups. At end of 4 weeks, no Significant difference between lipid parameters. TC, mg/dL Week 0 / Week 4 / % change Oat bran 286 / 274 / -4.1 Wheat bran 297 / 286 / -3.9 LDL % change from baseline Oat bran +10.3 Wheat bran +8.7 Mean body weights did not change during the oat period but decreased significantly during the wheat period.	There was no measure of dietary soluble fiber. Subjects increased consumption of PUFA and decreased intake of saturated fat (all NS) during test period. Investigators accounted for ↑ in fat consumption as due to use of PUFA margarine with bread. Oat bran bread was no better than wheat bran bread on lowering serum CHOL when subjects were on AHA diet. Small sample size.
Leadbetter J. et al., 1991 (Ref. 83)	Intervention, randomized, not blinded.	40 men and women, ages 25 to 64 (TC 250 to 348 (mg/dL), free-living.	A four-by-four Latin square design; Subjects added 0, 30, 60, and 90 g/day oat bran to their usual diet for 1 month intervals. No washout between periods. Oat bran provided in weighed sachets and detailed advice and recipes were provided. Five-day food records were kept prior to study and single-day records were kept during study periods. Beta-glucan content of oat bran was 3.7 to 4.2%	Base diets (excluding oat bran): 0 g/d / 30 g/d / 60 g/d / 90 g/d Cal. 1854 / 1947 / 2017 / 2017 % Fat 36.6 / 34.7 / 33.5 / 34.8 % CHO 45.3 / 48.2 / 50.2 / 48.6 % Sat Fat 13.5 / 13.0 / 13.4 / 14.0 Fiber, g 27 / 23 / 26 / 24 Starch, g 64 / 86 / 93 / 99 Results: No s effect of OB at any dose on TC or LDL; no dose-related trend and no correlation between bran dose and change in CHOL conc. Oat Bran Intake, g/day 0 / 30 / 60 / 90 TC, mg/dL 278 / 284 / 279 / 273 LDL, mmol/L 4.77 / 4.65 / 4.85 / 4.58 HDL, mmol/L 1.56 / 1.49 / 1.49 / 1.42	Authors state that OB used in this study may be lower in SF content than the OB used in studies showing ↓ CH with OB supplementation. No dietary or body weight data.

TABLE-- CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Resnicow, K. et al., 1991 (Ref. 96).	Health survey, not controlled.	31 Seventh Day Adventist, ages 5 to 44 years (9 children 5 to 17 years; 27 adults 19 to 46 years); mean serum CH 131.5 mg/dL; free living.	Subjects chosen had not consumed food of animal origin (including meat, poultry, fish, eggs, milk or other dairy products) for at least 6 mo prior to study. Lipid levels were reported separately for children. There were no blood lipid values for omnivore controls, so derived these values from Lipid Research Clinics Population Studies Data Book for basis of comparing vegans and omnivore controls. Current food intake measured using a quantitative weekly consumption and typical portion sizes. Fiber intake for vegans: 45 g/day, controls: 20.	Results for adults only: vegans observed / expected / % differ,* mean values, mg/dL TC 139 / 162 / -23 LDL 81 / 116 / -30 HDL 54 / 50 / +8 * Statistical significantly not reported. Vegans had s lower daily intake of energy; % energy from fat (31% versus 38%), total fat, saturated fat, Monounsaturated fatty acid, and CHOL; and protein; also s higher intake of fiber.	There are multiple confounding factors not addressed in this survey. Exercise patterns, lifestyle, and body weight are just a few examples. Soluble and insoluble fiber were not assessed. Foods consumed in greater frequency by vegans: almonds, cashews, and their nut butters, dried fruits, citrus fruits, soy milk and greens. These foods contributed almost 40% of daily energy (only 7% for controls).

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Spiller, G. A. et al., 1991 (Ref. 97)	Intervention, randomized, cross-over.	13 male and females, 62 ± 3.0 years, TC 204 to 276 mg/dL, free living	Three-day food record kept during baseline period and during 3rd week of treatment. Each treatment dose was preweighed in pouches; 3-week supply given to subjects at start of each test period. Both fiber were mixed with water or other fluid and consumed before each meal. Subjects remained on regular diets. Test periods: 21 days then cross-over to other fiber for 21 days. Blood lipid values made on days 14 and 21during treatment period and on days 14 and 16 after treatment stopped. Fiber sources: guar gum: 15 g/day providing 11 g/d dietary fiber and 10g/d SF; oat fiber source: 77 g/d providing 11 g/d dietary fiber and 5 g/d SF, 3.3 g ß-glucan.	TC / LDL / HDL (mg/dL) Baseline 244 152 62 Guar at day 14 217 124 63 day 21 219* 126* 63 Oat bran at day 14 235 142 62 day 21 236 143 62 * Significant from baseline. Guar : 11% ↓ TC Oats: 6% ↓ TC	Study needs control group. Changes in TC for both treatment groups took place within 14 days with no significant changes taking place between days 14 and 21. Limitations of study: Short test period. No washout between test periods. Baseline diets and dietary intake during treatment periods not reported; total dietary soluble fiber was not reported. Small sample size. No dietary data. No weight changes. Both guar and oat fibers consumed before meals--- not typical dietary intake.
Cara, L. et al., 1991 (Ref. 84)	Intervention.	10 men and women (8 women), 35 to 68 years, TC 254 to 367 mg/dL, 6 had mild to severe hypertriglyceridemia, free living.	Subjects consumed regular diet for one week as baseline period, followed by 4 weeks on 30 g wheat germ (2.9 g dietary fiber), then 4 weeks on regular diet with no supplementation. Base diet monitored by 7-day food recall; 30day food recall during last week of test period. Base diet: pro. 14.4% energy; fat 35.9%, refined CHO 8.7%, complex CHO 41%, dietary fiber 13.6 g/d, alcohol 6g/d.	Baseline / Wheat Germ / Follow up TC, mg/dL 302 276* 284 LDL, mg/dL 191 189 195 HDL, mg/dL 41.5 47 50 * Significant from baseline TC after final 4 weeks with no wheat germ not significantly different from baseline.	No control. Small sample size, no reporting of dietary soluble fiber and saturated fat in diet during baseline and treatment periods. Authors speculate that the protein content of wheat germ (high in vegetable protein) could account for the results observed. No saturated fat data.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Kawatra, A. et al., 1991 (Ref. 88).	Intervention.	20 overweight men and women (bodyweight 10% higher than standard Weight for Height of Life Insurance Company India), TC 172.5 to 277.5 mg/dL, free living.	Subjects added 15 g guar gum to normal diet for 6 weeks. 10 g of guar was consumed in form of salted biscuits and 5 g was mixed with flavored drink 10 to 15 minutes before main meal. 1/5 of normal diet was collected for 3-days prior to start of test period and during the last week of the test period and analyzed for nutrient composition.	Baseline / Final / %change TC, mg/dL 212 / 176 / ↓16.7* LDL, mg/dL 144 / 105 / ↓26.5* HDL mg/dL 54.8 / 55.4 / ↑1.5 TC/HDL 3.9 / 3.2 / ↓13.7%* * significant.	Total dietary fiber, dietary soluble fiber and saturated fat were not reported. No body weight data.
Tinker, L. F. et al., 1991 (Ref. 89)	Intervention, randomized, cross-over, Subjects acted as own controls.	41 men, ages 29 to 79. TC 201 to 290, free living. 6 had history of cardiovascular disease or CV surgery.	Dietary records made from self-reported food records collected every other day for 2 weeks prior to test Food records kept during test periods. Subjects consumed wither grape juice (GJ) (369mL/day) or 12 prunes (PR) (100 g/d) for 4 weeks, followed by additional 4 weeks. 100 g of prunes provides 6 to 7 g DF, of which approximately 60% is pectin.	Base diet / GJ diet / PR diet Energy 2522 / 2572 / 2579 Pro, % 16 / 15 / 14 Fat, % 33 / 30 / 30 CHO, % 47 / 51 / 51 alcohol, % 4 / 4 / 5 CHOL, mg 276 / 255 / 277 DF, g 21 / 18 / 24 TC, mg/dL 226 / 230 / 226 LDL, mmol 3.89 / 4.09 / 3.92 HDL, mmol 1.30 / 1.27 / 1.26 There was no difference in TC levels between baseline diet & prune diet. Percent of energy from CHO on GF and PR diets increased, % fat and Pro decreased. Fiber intake increased on PR diet, decreased on GJ diet.	Authors compared results of prune diet to grape juice noting that plasma cholesterol tended to be lower at the end of the prune period, although not statistically significant.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Karlander, S. et al., 1991 (Ref. 85)	Intervention, controlled, randomized, cross-over.	13 men and women with NIDDM, mean TC 275 mg/dL, free living. 5 were on chronic treatment with beta-blockers and diuretics because of hypertension; 8 were only on diet treatment with sulfonylurea (SU).	Study was divided into three 6-week periods: a run-in period and 2 study periods. Run in period: subjects given routine dietary counseling glucose control. Subjects then randomized to start fiber-rich diet or continue with regular diet(control). After first test period, subjects switched to other diet. Medications were left unchanged. Diet history and weights were taken every 3rd week. Dietary advice: energy reduction for obese patients—CHO 55% energy, fat 30%, Pro 15%. Fiber: best fiber—20 g Fibrex/day (16 G DF) divided into thirds and taken with each meal. Diet history showed base diets: 44% energy as CHO, 40% fat, 16% Pro, mean DF in control diet and SU-tx patients was 18 g/day. TDF during test period was 34 g/day.	During run-in period SU tx group had S loss in body mass index; no other weight loss occurred with either group during the test periods. Diet group / SU group TC, mg/dL fiber 278 / 247* control 275 / 275 * Significant difference from SU control group.	Cholesterol lowering (10%) only in patients treated with SU. Authors state that hypocholesterolemic effect of this magnitude appears to be common during fiber treatment of NIDDM. Authors also note that another study noted a similar effect of guar in insulin-treated, but not SU-treated patients with NIDDM. They conclude that this suggests that a hypocholesterolemic effect of fiber in NIDDM patients is not linked to the type of treatment but may be explained by patient selection. Beet fiber had no effect on serum triglycerides or in this study. No body weight data.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Isreaolsson, B. et al., undated (Ref. 86)	Intervention, placebo controlled, double-blind, cross-over.	27 women, 55 to 56 years, TC 263 to 297 mg/dL, free living, selected from health screening program concerned with cardiovascular disease risk factors and the effects of high alcohol consumption.	One month run-in period on a moderate cholesterol, low fat diet with increased ratio of PUFA/SPA; followed by randomized assignment to intervention or placebo group for 1 month, then cross-over. Placebo(bread crumbs or bread crumbs with bread) 30 g/day (3.5% fiber). Best fiber (crumbs packed in 5 g portions or as bread with 3 g fiber/slice) 30 g/day. Diets provided between 1415 to 1494 Cal, 17 to 19.7% Pro, 27.6 to 26.9% fat. Total fiber 11.7 to 14.7 g/day (low fiber periods) and 33 to 34 g/day (high fiber periods).	Compared to placebo, beet fiber reduced serum cholesterol S after 2 weeks. After 4 weeks, the difference was not significant. MEAN DIFFERENCE AFTER INTERVENTION (Fiber minus Placeb0) mg/dL TC LDL HDL After 2 weeks w/ fiber: -10.0* -8.5 -3.1 After 4 weeks: -7.7 -11.6* +4.3	Subjects made changes to their diet after the run-in period by significantly decreasing their intake of alcohol. No report on the intake of dietary fat, especially the amounts of saturated and polyunsaturated fat consumed during test periods. Soluble fiber intake from diets not reported. Subjects on fiber consumed S more CHO. Limitations of study: short duration of study. No body weight data.
Kirston, R. et al., 1989 (Ref. 97).	Intervention, controlled.	13 men and women (7 with type IIa and 6 with type IIb hyperlipidemia), mean age 57.2 yrs, mean TC 286 mg/dL, free living.	Study was divided into three phases: a 30-day pretreatment observation phase, 60 days of treatment, and 60 days of post-treatment observation. During test period subjects consumed 4 g of guar with water before each main meal (total of 12 g guar/day). Subjects instructed to avoid cholesterol-rich foods during thestudy.	PreTx Tx TC, mg/dL 286 251* LDL, mg/dL 213 186* HDL, mg/dL 48 44 * Significant compared to baseline Total cholesterol, LDL and HDL all returned to baseline 60 days after cessation of treatment.	Sample size was small. Dietary intakes were not reported. No control group.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Jenkins, et al., unpublished (Ref. 94) .	Intervention, randomized, cross-over controlled feeding.	11 normal subjects (6 men, 5 postmenopausal women) with mildly increased blood cholesterol. (mean = 242 mg/dL) (3 Type IIa, 7 Type IIb, 1 Type IV), free living.	After a 2-month treatment with the AHA Step 2 diet, S? randomized to a high soluble fiber diet (SF) or a high insoluble fiber (IF) diet for first test period. Test period 1 to 16 weeks; 2-month washout on Step 2 diet only; cross- over to test period 2 to 16 weeks. Step 2 diet: ≤20% kilocalories total fat, 20% Pro, 60% CHO, <50 mg cholesterol. The SF diet provided fiber from beans, peas, lentils, barley, oat bran, and psyllium enriched cereal. Ss received foods from the clinic, but lived at home SF diet provided 16 g SF/d and 37.5 g/d IF. IF diet provided 12.8 g SF/d and 42.1 g/d IF.	Both diets (SF and IF) reduced total and LDL cholesterol. SF diet reduced total cholesterol by 6.3% and LDL cholesterol by 8.6% compared to the IF diet. Insoluble Fiber Diet Baseline / After 16 Weeks TC, mg/dL 242 226 LDL, mg/dL 163 152 Soluble Fiber Diet TC, mg/dL 257 211* LDL, mg/dL 172 139* *significantly lower compared to IF diet.	Well controlled study. The *soluble* and *insoluble* fiber diets differed by less than 4 g of SF, on average. The authors speculate that either current analytical methods may actually underestimate SF, of that IF may have some hypolipidemic effect from certain components such as lignin. They also note that some SF have no hypolipidemic effect (acacia, agar). Authors encourage consumption of fiber sources known to lower TC.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Jenkins et al., unpublished (Ref. 93)	Intervention, controlled feeding study with randomized, cross-over design.	12 hyperlipidemic subjects (3 men, 9 postmenopausal women), ages 38 to 70, mean TC--272 mg/dL, mean LDL-- 192 mg/dL.	Subjects consumed a Step 2 basal diet (see study above) for 2 months then randomized to receive either psyllium or wheat bran cereal. Test period 1 to 4 weeks; 2-week washout on Step 2 diet; Test period 2 to 4 weeks. Patients received their food from the clinic, but lived at home during the study. The psyllium cereal diet provided 16.2 g/d of SF, while the wheat bran cereal diet provided 9.5 g/d SF. Subjects in the psyllium group ate 9.35 g of psyllium/day.	The psyllium cereal diet significantly reduced TC and LDL cholesterol, while the wheat bran diet did not. PSY diet: Week 0 4 mg/dL Total CHOL 275 249* LDL 199 173* Control diet: Total CH 268 257 LDL 186 182 *Significant $p < 0.05$. In individuals with increased cholesterol and triglycerides in this study (Type IIb), the psyllium cereal diet did not reduce serum LDL cholesterol, while it was effective in Type IIa (elevated cholesterol without elevated triglycerides).	Small sample size. Well controlled study. Psyllium containing cereal was shown to significantly reduce serum total and LDL cholesterol. The effect was independent of a low fat diet. No significant difference between groups for TC/HDL, LDL/HDL, apo B/A1. Preliminary results also suggest that psyllium cereals may not effectively lower LDL cholesterol in individuals with concomitantly elevated triglycerides (Type IIb). Subjects ate 9.35 g of psyllium per day (>3 ounces of cereal).

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Anderson, unpublished (Ref. 95)	Intervention, randomized, double blind, parallel.	44 men and women, mild to moderate hypercholesterolmec (TC 200 to 300 mg/dL), free living.	Subjects (Ss) were followed for 7 weeks. Week 1 was baseline period when subjects consumed their usual diets. Then Ss randomized to receive psyllium (PSY) cereal or wheat bran cereal and instructed on Step 1 diet and asked to adhere to it for 6 weeks. Step 1 diet: 55% total energy as CHO; 15% as protein; 30% as fat, less than 10% as saturated fat, and less than 300 mg cholesterol/day. Ss returned to clinic after 2, 4, 4, and 6 weeks on cereal. 3-day diet records were kept during week 3 of test period. Ss consumed 4 ounces of cereal (2 ounces in morning and 2 in evening). PSY cereal provided 11.4 g PSY, 24 g TDF, 12 g SF. Wheat cereal provided 20g TDF and negligible SF.	PSY group TC significantly ↓ (8%) 251 to 230 mg/dL compared to baseline and significantly lower than wheat group. LDL ↓ significantly (13%) in PSY group compared to baseline. No significant changes in wheat group.	Average consumption of psyllium cereal was 3.7 ounces/day
Earll et al. unpublished (Ref. 90)	Intervention.	7 men and women, hyperlipidemic (TC 261 to 346 mg/dL), free living, ages 32 to 71, treated by physician for (average) 2.4 years for hyperlipidemia.	Each subject served as own control. Ss were asked to take 24 g of fiber/day for 6 weeks and 48 g/day for 6 more weeks. At week 20 (8 weeks after test period ended), Ss had another blood lipid test. Ss instructed by dietitian on how to incorporate fiber into their diet and how to keep diet records. Diet records were kept for 3 days at the start, after 6 weeks, and again after 12 weeks. Corn fiber (milled and ground) provided 89% dietary fiber and less than 2% SF. Ss mixed the fiber with water. No indication when fiber was consumed during the day.	Mean fiber consumption for first 6 weeks was 22.7 g/day; for second 6 weeks—41 g/day. Two Ss stated that they could not consume 6 packets per day for 6 weeks so continued with 3 packets/day. Total cholesterol was significantly reduced on an average from 298 to 253 mg/dL, although much smaller changes were observed in two Ss and one subject had an increase in TC. TC returned to baseline after the 8-week followup period when there was no intervention. There was no significant effect on HDL. LDL was not reported.	Total dietary fiber, total SF, dietary saturated fat before, during, and after test period were not reported. Small number of subjects in this study. The serum cholesterol for all Ss except 1 remained above 200 mg with fiber intervention. No control group. No body weight data.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Wolever et al., unpublished (Ref. 101).	Intervention, randomized, controlled, cross-over.	42 subjects (21 men, mean age 55 years; 21 women, mean age 58 years), 14 Ss were on lipid lowering drugs, 3 had type 2 diabetes.	Subjects were tested for 2-week periods separated by a 2-week washout period. The base diet was an AHA Step 2 diet. During test period Ss asked to consume 2 servings of breakfast cereal daily: one in morning and one in evening. The test and control cereals were matched for energy and fed at a dose of 60 g/day. Psyllium (PSY) cereal provided 6.7 g/d of psyllium.	After 2 weeks of PSY: Baseline / Test TC, mg/dL 261 / 244* LDL, mg/dL 183 / 168* HDL, mm/L 1.14 / 1.10* * Significantly different from baseline.	Subjects were consuming Step 2 diet which restricts fat to less than 20% of calories. Subjects consuming lipid lowering drugs had decreased TC of 6.1% and LDL of 4.7%, not statistically significant from diet alone group. The short test period of 2 weeks of this study limits the usefulness of the results.
Wolever et al., unpublished (Ref. 102).	Clinical trial to evaluate the effectiveness of psyllium taken in foods versus psyllium taken between meals.	18 subjects (9 men and 9 women), mean age 54 years; 2 Ss were on lipid lowering drugs.	Study design with three 2-week test period separated by 2-week washout periods. Ss all consumed AHA Step 2 diet prior to study. Three treatment periods: Ss provided with cereal were asked to consume one with breakfast and one with dinner; Ss asked to consume PSY cereal between meals; Ss asked to consume control breakfast cereal. PSY cereal provided 6.7 g TDF per day from psyllium and 23.1 g/d TDF from the cereal. The control cereal provided 23.2 g/d TDF.	PSY with meals: Control / PSY TC, mg/dL 259 / 237* LDL, mg/dL 185 / 164* PSY between meals: Control / PSY TC, mg/dL 259 / 251 LDL, mg/dL 185 / 174 * Significantly different from control.	The 2 week period of this study limits the usefulness of the results.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Spencer and Coo(?) unpublished (Ref. 109)	Intervention, cross-over, blinded, placebo used.	31 male, serum cholesterol between 200 to 270 mg/dL.	A 6-week test period. Test subjects consumed 20 ounces of a fiber-supplemented juice per day to the regular diet, which supplied 10 g of DF (70% soluble fiber, predominantly from gum arabic) Placebo group received 20 ounces per day of nonsupplemented apple juice. Ss were asked to maintain normal eating and lifestyle habits.	With both ordered groups totaled, there is a significant decrease in serum total cholesterol and LDL–cholesterol during the period of consumption of fiber-enriched juice.	The cholesterol intake was significantly higher in the juice only group. In the group, ordered plain juice, then fiber-enriched juice, there is no change in total serum cholesterol followed by a significant decrease while on fiber-enriched juice. In the group which was given fiber-enriched juice, followed by no increase while on plain juice. The authors attribute this to a carryover effect of the fiber, but this is difficult to say.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Neal and Balm, 1990 (Ref. 98).	Intervention, parallel, open-label, clinical trial.	59 subjects with total cholesterol between 215 and 396 mg/dL.	29 subjects were assigned to dietary intervention only; 30 subjects were assigned to dietary and psyllium intervention. During the first 7 weeks, all subjects were to adapt to the AHA phase I diet. The subjects who were in the diet plus psyllium group were instructed to take psyllium in the form of Metamucil immediately after breakfast, and immediately after the evening meal for a 13-week period.	Dietary response period: During the first 7 weeks, men had significant lowering in their total serum cholesterol; women experienced very little change. After the treatment period, the PSY group had 5.5% additional decrease (significant) in TC compared to diet only group after the treatment period. Although there was a 5.1%↓ in LDL in PSY group compared to control, this decrease was not significant. Total Cholesterol(mg/dL): (After diet / Final / Avg Individual% Change) Control 263 261 -1.6 PSY 266 247 -7.1* LDL Cholesterol(mg/dL): Control 182 176 -3.5 PSY 190 172 -8.6* * Significant from post diet.	Although the compliance to the diet was checked, the breakdown of nutrients and amount of total soluble finer, total fat and saturated fat were not reported for each group. During the 7 weeks pretreatment period, results showed the women's TC did not respond to the AHA diet. Small weight loss in both groups.
Uusitupa et al., 1989 (Ref. 100).	Randomized, double-blind parallel group.	39 patients with NIDDM, mean age 58.6--men and 61.4 years—women, mean TC 253 mg/dL; all 39 subjects were on drug treatment for diabetes, 15 were on antihypertensives, 7 Ss were on drug treatment for coronary heart disease, and 6 Ss were on drug treatment for both hypertension and coronary heart disease, free-living.	Ss were randomly assigned to test or control groups. Group A: Received 5 g guar gum three times per day before meals. Group B: Received 5 g wheat flour three times per day before meals. After 3 months, group B switched to guar gum for the remaining 10 months of the study, and group A continued on guar. Ss advised to lower fat calories to 35% and increase carbohydrates to 50% of calories.	Serum total cholesterol (mg/dL) (run-in / 3 mo / 12 mo) A: 253 220 237 B: 253 242 233 There is a significant difference between the guar gum group and the control at 3 months.	Significant weight loss occurred, but in both the control and treatment groups to a similar degree. Authors question compliance of Ss during months 4 to 12 because serum cholesterol increased in both groups. Group B showed highest serum cholesterol at month 11 (242 mg/dL). Diets during the test period were not reported. Total soluble fiber, total fat, and saturated fat were not reported.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
O'Connor et al., in press B302 (Ref. 103)	Multicenter (7), double-blind, randomized, parallel group, placebo controlled trial.	Males and females (169 randomized, 135 completed study), between the ages of 18 and 70 years with a diagnosis of mild to moderate primary hypercholesterolemia.	Step one diet for 9 weeks; 15-week test period. Five Fiber Supplement (FFS) packet consists of 7.5 g SF (guar and pectin) and 2.5 g of IF. Placebo packet consists to 5.2 g of IF, no soluble fiber. During Week 1 of supplementation, Ss took 1 packet FFS per day, before dinner. During Week 2, they alternated days between one packet per day before dinner. During weeks 3 to 15, Ss took two packets of FFS per day, one before breakfast and one before dinner. Ss assigned to the two packet (26.4 g) group received FFS for all doses during Week 1 through Week 15. Ss who were assigned to the placebo group received placebo treatment for all doses during weeks 1 to 15.	Percent change in fiber from baseline minus % change in placebo from baseline: Week TC LDL-C 3 -9.0 -12.7 4 -7.8 -10.3 9 -8.7 -11.8 12 -6.2 -10.3 15 -6.8 -10.2 All values are significant.	Tightly-controlled trial. Dietary factors well-controlled; all major nutrients kept constant except for fiber.

TABLE-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
O'Connor et al., in press B301 (Ref. 103).	Multicenter (4) double-blind, randomized, parallel group, placebo controlled trial.	Males and females (161 randomized, 127 completed study), between the ages of 18 and 70 years with a diagnosis of mild to moderate primary hypercholesterolemia	Step 1 diet for 9 weeks; 15-week test period. Five Fiber Supplement consists of 7.5 g SF (guar and pectin) and 2.5 g of IF. Placebo consists to 5.2 g of IF, no soluble fiber. During Week 1 of supplementation, subjects took one packet of treatment per day, before dinner. During Week 2, they alternated days between one packet of treatment per day before dinner, and two packets of treatment per day, one before breakfast and one before dinner. During weeks 3 to 15, Ss took two packets of treatment per day, one before breakfast and one before dinner. Ss who were assigned to the one packet (13.2 g) of Five Fiber Supplement group received active treatment with the dose before dinner each day. The dose before breakfast dufing Week 2 (as required) and during Week 3 throught Week 15 was placebo. Ss who were assigned to the two packet (26.4 g) group received active treatment for all doses during Week 1 through Week 15. Ss who were assigned to the placebo group received placebo treatment for all doses during weeks 1 to 15.	Percent change from baseline in "Relative Efficacy" over time (relative to placebo). Week / 1 Packet Supplement LDL-C / 2 Packets Supplement LDL-C 3 / -7.6 / -12.0 6 / -9.3 / -13.8 9 / -4.5 / -7.5 12 / -4.2 / -8.6 15 / -5.9 / -7.9 All values are significant for the two-packet group. Week / TC / TC 3 / -5.2* / -6.9 6 / -5.0* / -8.8 9 / -2.4 / -4.3 12 / -2.2 / -4.7* 15 / -3.6* / -5.3* * Significant difference.	Well-controlled, free-living, trial. Dietary factors well-controlled. All major nutrients kept constant except for fiber. A dose-response was not statistically demonstrated bewteen placebo, one-packet dosage and two-packet dosage.
O'Connor et al., in prose (Study B301 extension) (Ref. 103)	An open-lable study of the safety and efficacy of Five Fiber Supplement administered twice a day in conjunction with a low fat diet for 36 weeks.	Patients who completed 15 weeks of treatment with either one packet of Five Fiber Supplement per day, two packets of Five Fiber Supplement per day or placebo were eligible to continue therapy with two packets of Five Fiber Supplement per day for an additional 36-week period. 102 entered and 59 completed the 36 additional weeks.	During this open-label extension, patients were continued on their Step 1 Diet. During the first week of the extension, patients took one packet of treatment per day (before dinner). Thereafter, during weeks 17 to 51, patients took two packets of treatment per day (one before breakfast and one before dinner).	During the 36-week extension of the trial, total cholesterol was maintained at 5.3% (Significant) and LDL-cholesterol at 8.4% (Significant) lower than baseline.	This extension to the above study was not blinded by definition. The study was well-controlled for dietary factors and other major confounders.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Whyte et al., 1992 (Ref. 104)	Intervention, randomized with cross-over	23 men, mean age 45 years, mild hypercholesterolemia (TC 209 to 259 mg/dL), free living.	Subjects were randomly assigned to either the wheat cereal group or the oat cereal group after a 3-week baseline diet. During baseline period, all Ss consumed wheat cereal. Preweighed package of cereal were provided: 54 g of wheat bran per day; 123 g oat bran per day. Base diet was typical Australian diet with approximately 30 to 34% of calories as fat. Ss instructed on how to keep dietary records, measure and restrict fiber (so all Ss would have approximately same total fiber intake of less than 30 g/d. Each fiber cereal (2 servings/day) was consumed for 4 weeks followed by cross-over to other fiber cereal for an additional 4 weeks. Oat cereal: 10.3 g/d SF Wheat cereal: 3.4 g/d SF All diets: TDF approximately 27 g/d. Oat diets provided 71 g/d starch; wheat diets provided 42 g/d starch.	Data analysis showed no effect of treatment order. mg/dL / Base-line / Oat / Wheat TC 226 218* 228 LDL 159 150* 159 * Significantly compared to both baseline and wheat period.	Consumption of total fat and saturated fat during both test periods was about the same (35.5 g fat/1,000 kilocalories and 12.7 to 13 g saturated fat/1000 kilocalories). Short test period. No dietary cholesterol intake data.
Niemi et al., 1988 (Ref. 99)	Double-blind, cross-over trial with placebo.	22 subjects: 16 women, 6 men; with poorly controlled type 2 diabetes. Ages 40 to 76. Mean serum cholesterol 235 mg/dL and 255 mg/dL. 19 subjects on medication.	The study consisted of two 12-week treatment periods separated by 4-week washout period. Eleven patients, selected at random, started with microcrystalline cellulose during the first 12-week treatment phase followed by treatment with guar gum in the second 12-week period. In the other 11 subjects, the sequence was reversed. Both types of fiber were taken with meals three times daily. The initial dose was 5 g/day, which was increased up to 15 g/day during the 2-week period at the beginning of each treatment phase.	The pooled data show that serum cholesterol was significantly lower after 12 weeks on guar gum, but no significant change was found after cellulose. Serum cholesterol (mg/dL) Time / Cellulose / Guar Start 235 255 12 weeks 240 228* * Significant from start.	Although patients were advised to keep their normal diet, no measurements of diet (total soluble fiber, total fat and saturated fat, etc.) were discussed to verify this. Only the pooled data was reported. It would be helpful to examine the response of each group separately. Is cellulose and appropriate control?

TABLE—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Cerda et al., 1988 (Ref. 105).	Intervention, double-blind, cross-over with placebo.	27 subjects: 9 men, 18 women, ages 27 to 69 years. Mean serum cholesterol 275 mg/dL (range of 208 to 420 mg/dL, free living.	A 16 week study: 4-week baseline, 4 weeks on placebo or pectin, 4-week washout, then cross-over to 4 week on placebo or pectin tablets. Ss consumed normal diets but consumed 27 tablets (9 at each main meal) daily during test periods. Dietary records were kept during weeks 1, 7, and 16. Each Ss served as own control. Grapefruit Pectin: 15 g/day Placebo (flour): 15 g/day.	Baseline / Pectin / Placebo (mg/dL) TC 275 / 254* / 275 LDL 195 / 174 / 191 HDL 41.6 / 41.1 / 41.5 * Significant from baseline and placebo.	Authors reported good compliance to tablet consumption. The subjects dietary intake of calories, total fat, saturated fat, cholesterol, and soluble fiber were not reported. Short test period. No body weight data.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Haskell et al., 1992 (Ref 106).	Intervention, randomized, double-blind, placebo-controlled trials.	Total cholesterol range for all studies: 200 to 280 mg/dL Study (S) 1: 58 men and women, mean age 57 yrs. S 2: 40 men and women, mean age 56.4 yrs S 3: 16 men and women, mean age 52.5 yrs S 4: 49 men and women, mean age 56.3 yrs. All free living subjects.	After baseline period Ss randomly assigned to one of 4 studies: S 1: 12-week test. Evaluated CH-lowering properties of mixed SF with 56% from acacia gum. Fiber product: powder mixture of acacia gum (9.7 g), psyllium (4.9 g) and guar gum (2.6 g)for a total of 17.2 g/day divided into 3 servings/day. All placebos consisted of 15 g of fructose. S 2: 4-week test. 15 g/day acacia gum powder divided into 3 servings/day. S 3: 8-week cross-over using guar as control. Test fiber mixture: pectin (3.9 g), psyllium (6.3 g), guar (3.3 g), and locust bean gum (1.5 g) for total of 15 g/day SF given in 3 servings per day; guar control: 10 g guar and 1 g pectin for total of 11 g/day given in 3 servings/day. S 4: 4 weeks. A dose-response study with SF test mixture used in S 3. Mixtures tested: 1 svg/d 2 svg/d 3svg/d pectin, g 1.3 2.6 3.9 psyllium, g 2.1 4.2 6.3 guar, g 1.1 2.2 3.3 locust bean, g 0.5 1 1.5 Total g/day 5 10 15	S 1: There were no statistically significant changes from baseline to 6 or 12 seeks within or between groups. S 2: Baseline 4 weeks %change* TC mg/dL placebo 264 269 ↑1.9 acacia 266 265 ↓0.4 LDL placebo 200 206 ↑3.3 acacia 194 195 0.0 HDL placebo 55 52 ↓5.4 acacia 60 58 ↓3.9 * not statistically significant from baseline. S 3: Baseline 4 weeks % change TC guar 249 225* ↓2.7 fiber mix. 249 230* ↓8.3 LDL guar 184 163* ↓13.6 fiber mix. 184 166* ↓12.4 HDL guar 54 50** ↓6.5 fiber mix. 54 51** ↓5.9 *Significant from baseline $p<0.01$ ** Significant from baseline $p<0.05$. S 4: Baseline 4 weeks % change TC placebo 261 262 0.3 5 g/d 255 242 ↓5.2 10 g/d 259 247 ↓0.9 15 g/d 275 242* ↓12.2 LDL placebo 184 186 0.0 5 g/d 186 176 ↓5.6 10 g/d 187 174 ↓6.8 15 g/d 211 179* ↓14.9 HDL placebo 67 62 ↓6.4 5 g/d 57 54 ↓6.1 10 g/d 61 62 ↑1.9 15 g/d 53 48 ↓9.4	Subjects' diets were not reported. Short test periods.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Nervi et al., 1989 (Ref. 107).	Purpose of study was to evaluate hypothesis that legumes may be a dietary risk factor for cholesterol gallstone formation in Chileans. Nonblinded cross-over intervention study.	20 young Chilean men, ages 10 to 22 years, mean TC 162 mg/dL.	Subjects received a control diet for 25 to 30 days. Food preparation and intakes were controlled by nutritionists. Diets eaten for 6 days a week; Ss were allowed free food intake on Sumday. Test period was 30 to 35 days on a legume diet: beans 4 days, peas 2 days, lentils 1 day. Ss control and test diets were matched for calories, protein, fat, fiber and cholesterol intakes. Control Legume Diet Diet Energy, Cal 3219 3219 % of Calories Protein 14 14 Carbohydrate 54 53 Fat 32 33 Cholesterol, mg 300 302 Total Fiber, g 12.4 12.5S	Serum cholesterol (mg/dL) Control Diet Legume diet 162 143 Difference is significant (p<.001).	Short test period. Authors reference a study that indicates that epidemiogogical studies have demonstrated increased prevalence of gallstones in men ingesting a diet that lowers serum cholesterol. No saturated fat intake data. No body weight data, low baseline serum cholesterol.
Unpublished study submitted with comments (Ref. 100)	Double-blind double cross-over intervention.	23 healthy men, Age > 18 years, TC > 240 (exact ages and total cholesterol not reported), free living.	Baseline period: 4 weeks Step I diet. Subjects randomly assigned to either psyllium-wheat bran-psyllium (n=12) or wheat bran-psyllium-wheat bran (n=11) for 8, 5 and 5 weeks respectively on each regimen (18 weeks total). Subjects were provided with boxes of cereal and instructed to eat 2 ounces of the study cereal in the morning and one ounce in the evening. The psyllium cereal had a total of 5 g of soluble fiber and 7.4 g of total dietary fiber per ounce. The wheat bran cereal had 1 g of soluble fiber and 5 g of total dietary fiber per ounce. Relative percentages of protein fat, sugar and starch in the two products were reported to be similar.	Effect of Psyllium versus Wheat Bran Cereal (in mg/dL) PSY WHEAT BRAN DIFFERENCE TC 225 235 4.3% LDL 148 157 6.1% HDL 46 46 - * Significantly different p<.0001.	It is difficult to evaluate the results of the study because the authors do not report the initial cholesterol values of either group, instead relying on differences between the groups' average cholesterol values. It is important to review the effect of the diet order, to observe any changes in going from one test product to the other, and note any temporal trends in rising or falling of cholesterol levels on each diet. No dietary data

TABLE-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Anderson et al.,1984 (Ref. 110).	Metabolic ward, study for 21 days with random allocation to groups.	10 male subjects age 66 to 66 with initial serum cholesterol > 260 mg/dL.	All subjects received the control diet for 7 days, and then were placed on a test diet for 21 days. Control diets provided 19% of energy as protein, 43% as CHO, 38% as fat 20 g plant fiber, and 6 g soluble fiber per day. The oat-bran diet provided 100 g of oat bran per day served as a bowl of hot cereal and five oat bran muffins per day. This supplied approximately 48 g total plant fiber and 18 g soluble fiber per day. The bean diet containing 100 g of dried beans per day provided the same amount of total plant fiber and soluble fiber as did the oat-bran diet. After controlled trial ended, subjects were given high-fiber maintenance diets to follow for an additional 24 weeks; four of the subjects were followed for a total of 99 weeks.	Mean serum cholesterol values of oat and bean groups: (values in mg/dL). TC LDL HDL **Week** 1 294 216 37.2 4 226 167 29.0 7 233 169 31.4 10 234 164 33.9 16 232 164 33.9 24 210 164 35.2 * Note: All values are significantly lower when compared to week 1. After 99 weeks of followup (free-living on high-fiber maintenance diets), serum chol values were 26% (p<.001) below initial values at 24 week and 23% lower (p<.003) at 99 weeks.	Small sample size. Significant weight loss during test period; no significant weight loss during control period. Short period. No control.

TABLE-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Fukagawa et al., 1990 (Ref. 114).	Metabolic ward study; clinical trial, nonblinded, no placebo. Young men only ate their meals on the metablic ward. The older group were admitted to the ward.	Six healthy male students, age 18 to 24 (TC 200 mg/dL) and six healthy older men and women, age 67 to 86 (TC 238 mg/dL).	The subjects were placed on a high fiber diet for a period of 21 to 28 days after consuming their usual ad libitum diet. High fiber diet: 68% of energy from CHOs, fat intake of 14%, protein of 18%; 33 g per 100 kilocalories of fiber. Plant fiber was provided by whole grain or grain cereals and breads(40%), vegetables such as beans, corn, or peas (20%), other vegetables (31%), and fruits (9%). Soluble fiber/day Reg. Diet High fiber younger group 3.5 g 23.6 g older group 3.7 g 17.1 g Ad libitum diet assessed by dietary recall.	Serum cholesterol in young and old subjects before and after 4 weeks of a high fiber diet: Before After mg/dL Both (n=12) 219 170 ↓22% Young (n=6) 200 147 ↓26% old (n=6) 238 193 ↓45% * All *after* values are significantly lower then corresponding *before* values.	Small sample size. There was no control group, fat was not controlled. The ad libitum diet was significantly higher in fat (37 to 42% versus 14% of calories), saturated fat (15 to 17% versus 3% of calories), and cholesterol (720 to 755 versus90 to 134 mg/d) than the test diet. Ad libitum diet relied on dietary history alone. It should be noted that the objective of this study was to examine the effects of a high fiber diet on insulin sensitivity; the cholesterol findings were secondary. No body weight data.
Turnbull and Leeds; 1987 (Ref. 111).	Clinical study, randomly allocated, cross-over.	9 men, 8 women, age 23 to 59, initial serum cholesterol level of at least 232 mg/dL, free living.	Subjects were placed on a one-month run-in period when they followed a low-fat diet (≤35% of calories from fat). Subjects were then randomly allocated to 1 month of an oat diet (50 g oats each day at breakfast and 100 g oats as biscuits or a wheat diet (37 g wheat biscuits each day at breakfast and 100 g wheat as biscuits. At the end of the month, subjects switched diets. Oat products provided 5.4 g SF/day. Wheat products provided 3.1 g SF/day.	Values for cholesterol before and after intervention: Initial Final Sig Change? mg/dL Oat period Total chol 232 220 Y LDL-chol 167 143 Y HDL-chol 46 54 NS Wheat period Total chol 228 232 NS LDL-chol 159 163 NS HDL-chol 50 50 NS	Fat intake is higher during oat period (this does not invalidate cholesterol-lowering effect of oats). No saturated fat or cholesterol intake data.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Walsh et al., 1983 (Ref. 117).	Clinical trial, double-blind, randomly-assigned, with placebo.	20 women, (ages not given), obese (20% or more over ideal weight), mean serum cholesterol 198 mg/dL.	The trial was of 8-week duration. The glucomannan group (GM) took two capsules of a supplement containing 500 mg of purified glucomannan, three times per day, with 8 ounces of water, 1 hour before each meal. The placebo group (PG) took two capsules containing 500 mg starch under the same conditions. All patients were instructed not to deviate from their previously- established eating and exercise patterns.	Changes in weight and cholesterol Weight Change (lbs) / Chol Change (mg/dL) Week 4 8 4 8 GM -4.9* -5.5* -20.9* -21.7* PG 0.4 1.5 5.9 4.7 Difference between groups. 7.0 lbs 26.2 * Significant difference between groups.	Because weight loss and cholesterol-lowering are closely correlated, it is not possible to conclude that the cholesterol-lowering effect is and independent result of glucomannan supplementation.
Anderson et al., 1992 (Ref. 118).	Intervention, randomized, double-blind, parallel design.	44 men and women, ages 25 to 70, total cholesterol 199 to 300 mg/dL, 80 to 130% of desirable body weight, free living.	One-week baseline period--Ss consumed usual diet then randomized to receive psyllium-flake or wheat-bran-flake cereal (control) for 6 weeks. Ss also instructed on step 1 diet and asked to adhere to this diet for 6 weeks. Wheat cereal: 28.4 g serving with 5 g total DF, negligible SF. PSY cereal: 28.4 g serveing with 6 g total DF, 2.9 g PSY, 3 g SF. Ss were instructed to consume one serving of cereal of the first day and add 28.4 g additional daily until a maximum of 114 g/day was reached. 114 g of PSY cereal would provide 24 g total DF, 11.6 g PSY, 12 g SF. Ss completed 3-day diet record during week 5 of treatment period.	Base Diets Wheat bran: Baseline Final / PSY: Baseline Final Energy (Cal) 1786 1899 1821 1723 Fat (% energy) 30.7 24.3 32.2 22.9 SF, g 5.6 5.9 6.1 15.1* * Significant difference from wheat group. Serum cholesterol, mg/dL TC 254 254 252 230+ LDL 174 174 170.5 149+ + Significant difference from baseline. Change in PSY group significantly different from change in wheat group.	Authors reported slight but significant decreases in body weight in both groups across time. However, there was no significant difference in weight loss between groups.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Braaton et al., unpublished (Ref. 119).	Intervention, randomized.	21 men and women, ages 43 to 64, hypercholesterolemic (mean serum cholesterol 255 mg/dL), free living.	Subjects consumed usual diets with the fat content adjusted to be at least 20% and preferably more than 25% of their daily caloric content. Three-day food dairy was used to record their diets before and during each treatment period. Instant soluble oat gum (3.6 g, 80% β-glucan) or placebo (maltodextrin) was mixed with noncarbonated diet fruit drink (250 mL) and consumed during each of the two main meals of the day for each 4-week period. There was a 2-week stabilization period prior to treatment, a 3-week washout period between treatments, and a 3-week washout period for the group on oat gum.	Dietary fat intake ranged from 30% to 31% of energy, total caloric intake was 2161 calories (stabilization period), 2069 calories (gum period), 1988 calories (washout), and 2077 calories (placebo period). Total Cholesterol Initial Final mg/dL Placebo 255 255 Oat gum 262 238* *Significantly different from baseline and placebo. LDL-Cholesterol mg/dL Placebo 174 176 Oat gum 180 154 During washout following oat gum treatment serum cholesterol increased from 238 to 258 mg/dL.	Total dietary soluble fiber, saturated fat and cholesterol intakes were not reported. During final washout following oat period, serum cholesterol returned toward pretreatment levels further supporting a true effect of oat gum. Short test period.
Bridges, S. et al., 1992 (Ref. 120).	Clinical Study, metabolic ward.	20 men, ages 38 to 73, mean serum cholesterol range of 252 mg/dL (wheat group) to 305 mg/dL (oat group).	Subjects received a base diet for 7 days followed by 3 weeks of oat bran or wheat bran supplementation. The base diet was a typical American diet composed of 43% energy from carbohydrate, 16% protein, 41% fat, and 450 mg cholesterol. Treatment = Tx; Pretreatment = Pretx; Total dietary fiber = TDF Fiber Intake on Diets Wheat Bran: Pretx Tx; Oat Bran: Pretx Tx TDF, g 18 34 19 34 SF, g 5.6 7.8 6.0 13.4 Oat bran and wheat bran were served as cereal or muffins.	Wheat Bran Oat Bran mg/dL Total CHOL Pretx 252 305 Tx 242 267* LDL-CHOL Pretx 130 167 Tx 123 146* *Significantly different from pretx period.	Control period of 7 days is inadequate. Pretreatment serum cholesterol was calculated from data presented. Serum cholesterol and LDL-cholesterol between groups is not well matched; oat group had such higher serum- and LDL-cholesterol than wheat group. Both groups experienced slight but significant weight loss. Not randomized; short test period.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Kashtan et al., 1992 (Ref. 121).	Intervention, randomized, metabolically controlled, parallel, double-blind.	84 subjects in two groups: group 1 to 42 men and women, mean age 61.3, with history of previous polypectomy; and group 2 to 42 men and women, mean age 51.2, with normal colon and colonic examination. Mean serum cholesterol of group 1: 207 mg/dL; group 2: 227 mg/dL.	Subjects were randomly assigned to either the oat bran group or the wheat bran (control) group. Subjects consumed the bran products twice a day for 2 weeks. All food was prepared and delivered to the subjects. Energy content of diet was one of four amounts: 1,600, 2,000, 2,400, and 2,800 calories Ss were fed the amount closest to their requirements based on the Lipid Research Clinics tables. Base diet: 37% fat, 16% protein, 47% carbohydrates; total dietary fiber-- 24 to 25 g/day. Oat bran supplement: 88.4 g/day: 11 to 17 g fiber; estimated 5 to 8 g SF Wheat bran cream of wheat: 73 g/day: 11to 17 g fiber/day.	Before After Change mg/dL Total CHOL Wheat bran 207 198** -0.25 Oat bran 227* 203** -0.63* LDL-CHOL Wheat bran 129 125** -0.11 Oat bran 150* 131** -0.48* *Significantly different from wheat bran. **Significantly different from baseline.	Soluble fiber consumption was not reported. Short term study--14 days.
Randhotra et al., 1989 (Ref. 122).	Intervention, self-controlled.	17 men, ages 37 to 60 years, hypercholesterolemic (mean serum cholesterol 224 mg/dL), free living. One subject had a history of heart attack and one subject was a type II diabetic.	A 6-week control period followed by a 6-week test period. Ss consumed their usual diet during the control period but maintained daily records of intake for first 4 weeks. Ss were provided a list of cereal-based and other foods identified as sources of SF and asked to consume these with their daily diets. Additional SF supplement of processed rice bran (30 g) and oat bran (30 g) was provided.	Nutrient Intake: Control Test Energy, Cal. 2378±431 2331±419 Fat, % energy 35.3±4.7 33.9±4.9 Saturated Fat,% 10±1.7 9±1.9 Total fiber, g 15.0±5.8 28.3±4.7 Soluble fiber,g 5.0±1.6 9.4±1.5 Ss individual data were reported. Six of the 17 Ss experienced lowered serum cholesterol of 1 to 17% compared to control value.	Statistical analysis not performed by authors. Results are too inconsistent in direction and magnitude to support an effect of SF on serum cholesterol. Some subjects failed to consume the supplement daily. Intake of both soluble and dietary fiber varied greatly among the participants.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Zhang et al., 1992 (Ref. 123).	Intervention, randomized, controlled, cross-over.	9 men and women (2 women, 7 men), ages 45 to 67 years, with ileostomies. Mean serum cholesterol--231 mg/dL.	The goal of this study was to elucidate the cholesterol-lowering mechanisms of oat bran and to compare the sterol excretion pattern on a basic diet (wheat flour bread, low fiber diet (LFD)) to oat bran (oat bran bread, highe fiber diet (HFD)). Subjects were randomly assigned to two groups (LFD or HFD) and each group followed for 3 weeks followed by cross-over to the other diet. Ss consumed the bread products with their own food which was modified to be low fiber. wheat flour bread: 4.9 g dietary fiber; oat bran bread: 29 g dietary fiber.	Serum Cholesterol mg/dL All Ss (n=9) LDF 214 HDF 194.5* Ss with low daily bile acid excretion (n=5) LDF 234 HDF 207* Ss with high daily bile acid excretion (n=4) LDF 189 HDF 179 *Significantly different from LFD.	Total dietary soluble fiber intake and intake of fat, saturated fat, and cholesterol were not reported. All subjects had ileostomies. Conlusions about fiber mechanisms in lowering serum lipids may not apply to the general population. Short test period.
Marlett et al., 1992 (Ref. 124).	Intervention, metabolically controlled, single isotope used to determine bile acid kinetics.	9 men, ages 20 to 28 years, normocholesterolemic (estimated range of 131 to 244 mg/dL).	A 2-month study: period 1: low fiber control period and period 2: high fiber period with oat bran. Base diets: energy--2,700, 3,000, 3,300, and 3,600 Cal/day with 35% fat, 15% protein, and 50% carbohydrate. Foods were consumed in a metabolic unit except an evening snack which could be taken home. Oat bran--100 g, provided 16.1% dietary fiber, of which 38% was β- glucan, and 46% was soluble fiber. Wheat glucan--an amount comparable to protein provided by oat bran was included in foods in the low fiber diet.	Low fiber Period / High fiber Period Mean dietary fiber intake: D.F.,g/day 16 33.9 S.F.,g/day 4.0 10.3 Serum Cholesterol mg/dL Prestudy / Low Fiber / High fiber 177 152* 138** *Significantly lower than prestudy value. **Significanlty lower than low fiber period. Total daily fecal bile acid excretion more than doubled when oat bran was incorporated into the metabolic diet: Total B.A., micromoles/day 476.4 1026.2	There were no changes in body weights. Small sample size.