ACTION: Notice of proposed rulemaking (NPRM); correction.

SUMMARY: This document contains a correction to the NPRM published in the **Federal Register** (63 FR 45912) on August 27, 1998. The NPRM proposes to ban, in certain domestic operations, the transportation of devices designed to chemically generate oxygen, including devices that have been discharged and newly manufactured devices that have not yet been charged for the generation of oxygen, with limited exceptions.

FOR FURTHER INFORMATION CONTACT: David L. Catey, (202) 267–8166.

Correction of Publication

In proposed rule FR Doc. 98–23010, beginning on page 45912 in the **Federal Register** issue of August 27, 1998, make the following corrections:

On page 45912, in the first column, in the heading, ''[Docket No. 29318; Notice No. 98–12]'', should read ''[Docket No. FAA–1998–4458; Notice No. 98–13]''.

In the **ADDRESSES** section on page 45912, in the first column, in the fifth line, the docket number ''FAA–98–29318'', should read ''FAA–1998–4458''.

In the Comments Invited section on page 45912, in the second column, last paragraph, first line, ''Docket No. 29318'', should read ''Docket No. FAA–1998–4458''.

Issued in Washington, DC on November 4, 1998.

Donald P. Byrne,

Assistant Chief Counsel.

[FR Doc. 98–30088 Filed 11–9–98; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 98P–0683]

Food Labeling: Health Claims; Soy Protein and Coronary Heart Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to authorize the use, on food labels and in food labeling, of health claims on the association between soy protein and reduced risk of coronary heart disease (CHD). FDA is proposing this action in response to a petition filed by Protein Technologies International, Inc. (the petitioner). The agency has tentatively concluded that, based on the totality of publicly available scientific evidence, soy protein included in a diet low in saturated fat and cholesterol may reduce the risk of CHD.

DATES: Written comments by January 25, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Susan M. Pilch, Center for Food Safety and Applied Nutrition (HFS–465), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–205–4500.

SUPPLEMENTARY INFORMATION:

I. Background

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) (Pub. L. 101–535). This new law amended the Federal Food, Drug, and Cosmetic Act (the act) in a number of important ways. One of the most notable aspects of the 1990 amendments was that they provided procedures whereby FDA is to regulate health claims on food labels and in food labeling.

In the **Federal Register** of January 6, 1993 (58 FR 2478), FDA issued a final rule that implemented the health claim provisions of the act (hereinafter referred to as the 1993 health claims final rule). In that final rule, FDA adopted § 101.14 (21 CFR 101.14), which sets out the rules for the authorization and use of health claims. Additionally, § 101.70 (21 CFR 101.70) establishes a process for petitioning the agency to authorize health claims about a substance-disease relationship (§ 101.70(a)) and sets out the types of information that any such petition must include (§ 101.70(d)). These regulations became effective on May 8, 1993.

In response to the 1990 amendments, FDA also conducted an extensive review of the evidence on the 10 substance-disease relationships listed in the 1990 amendments. As a result of its review, FDA has authorized claims for 8 of these 10 relationships, one of which focused on the relationship between dietary saturated fat and cholesterol and reduced risk of CHD. CHD is the most common, most frequently reported, and most serious form of cardiovascular disease (CVD) (58 FR 2739, January 6, 1993). Further, while the agency denied the use on food labeling of health claims relating dietary fiber to reduced risk of CVD (58 FR 2552), it authorized 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 CHD.

In the proposed rule entitled ''Health Claims and Label Statements; Lipids and Cardiovascular Disease'' (56 FR 60727, November 27, 1991), FDA set out the criteria for evaluating evidence on diet and CVD relationships. The agency focused on those aspects of the dietary lipid and CVD relationship for which the strongest scientific evidence and agreement existed. FDA noted that, because of the public health importance of CHD, identification of ''modifiable'' risk factors for CHD had been the subject of considerable research and public policy attention. The agency also noted that there is general agreement that elevated blood cholesterol levels are one of the major ''modifiable'' risk factors in the development of CHD. FDA cited Federal Government and other reviews that concluded that there is substantial epidemiologic and clinical evidence that high blood levels of total and low density lipoprotein (LDL) cholesterol are a cause of atherosclerosis and represent major contributors to CHD. Further, factors that decrease total blood cholesterol and LDL-cholesterol will also decrease the risk of CHD. FDA concluded that it is generally accepted that blood total and LDL-cholesterol levels are major risk factors for CHD, and that dietary factors affecting blood cholesterol levels affect the risk of CHD. High intakes of dietary saturated fat and, to a lesser degree, of dietary cholesterol are consistently associated with elevated blood cholesterol levels. FDA concluded that the publicly available data supported an association between diets low in saturated fat and cholesterol and reduced risk of CHD (58 FR 2739 at 2751).

Based on its review using the stated criteria, and on its consideration of comments received in response to the proposed rule entitled ''Health Claims; Dietary Fiber and Cardiovascular Disease'' (56 FR 60582), FDA concluded that the publicly available scientific information supported an association between diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products (i.e., foods that are low in saturated fat and cholesterol and that are good sources of dietary fiber) and reduced risk of heart disease (58 FR 2552 at 2572). In the 1993 dietary fiber and CVD final rule, in response to a comment regarding the apparent hypocholesterolemic properties of specific food fibers, FDA again articulated its criteria for evaluating diet and CHD relationships (58 FR 2552 at 2567). FDA agreed that

the effectiveness of naturally occurring fibers in foods in reducing the risk of CHD may be documented for specific food products. Further, the agency indicated that if manufacturers could document, through appropriate studies, that dietary consumption of the soluble fiber in a particular food has a beneficial effect on blood lipids predictive of CHD risk, they should petition for a health claim for that particular product. In response to two petitions that documented such evidence, FDA has authorized health claims for soluble fiber from certain foods and reduced risk of CHD in § 101.81 (21 CFR 101.81) (62 FR 3584 at 3600, January 23, 1997, and amended at 62 FR 15343 at 15344, March 31, 1997, and 62 FR 8119, February 18, 1998).

The present rulemaking is in response to a manufacturer's health claim petition on the relationship between soy protein and the risk of CHD.

II. Petition for Soy Protein and Reduced Risk of CHD

A. Background

On May 4, 1998, Protein Technologies International, Inc., submitted a health claim petition to FDA requesting that the agency authorize a health claim on the relationship between consumption of soy protein and the risk of CHD (Refs. 1 and 2). On August 12, 1998, the agency sent the petitioner a letter stating that it had completed its initial review of the petition, and that the petition would be filed in accordance with section 403(r)(4) of the act (21 U.S.C. 343(r)(4)) (Ref. 3). In this proposed rule, the agency presents the rationale for a health claim on this food-disease relationship as provided for under the standard in section 403(r)(3)(B)(i) of the act and § 101.14(c) of FDA's regulations.

B. Review of Preliminary Requirements for a Health Claim

1. The Substance Is Associated With a Disease for Which the U.S. Population Is at Risk

Several previous rules establish that CHD is a disease for which the U.S. population is at risk, specifically claims for dietary saturated fat and cholesterol and risk of CHD (§ 101.75 (21 CFR 101.75)); fruits, vegetables, and grain products and risk of CHD (§ 101.77 (21 CFR 101.77)); and soluble fiber from certain foods and risk of CHD (§ 101.81). FDA stated in these rules that CHD remains a major public health problem and the number one cause of death in the United States. Despite the decline in deaths from CHD over the past 30 years, this disease is still exacting a tremendous toll in morbidity and mortality (Refs. 4 through 6). There are more than 500,000 deaths each year for which CHD is an underlying cause, and another 250,000 deaths for which CHD is a contributing cause. About 20 percent of adults (male and female; black and white) ages 20 to 74 years have blood total cholesterol (or serum cholesterol) levels in the ''high risk'' category (total cholesterol greater than (>) 240 milligrams (mg) per (/) deciliter (dL) and LDL-cholesterol greater than 160 mg/dL) (Ref. 7). Another 31 percent have ''borderline high'' cholesterol levels (total cholesterol between 200 and 239 mg/dL and LDL-cholesterol between 130 and 159 mg/dL) in combination with two or more risk factors.

CHD has a significant effect on health-care costs. In 1985, total direct costs related to CHD were estimated at $13 billion, and indirect costs from loss of productivity due to illness, disability, and premature deaths from this disease were an estimated $36 billion (Ref. 4). Based on these facts, FDA tentatively concludes that, as required in § 101.14(b)(1), CHD is a disease for which the U.S. population is at risk.

2. The Substance Is a Food

The substance that is the subject of this rulemaking is soy protein (Ref. 1). Soy protein is an edible component of the soybean, *Glycine max*. Soybeans are a significant source of low-cost, high-quality protein in the human diet.

Soy protein is used as an ingredient in other foods. It is produced from raw whole soybeans by a multistep process that removes the lipid and indigestible components to concentrate the protein and increase its availability. Depending upon the particular steps used during processing, soy protein ingredients may take the form of isolated soy protein (ISP), soy protein concentrate (SPC), or soy flour (SF). Each of these ingredients may be further processed into texturized soy protein or texturized vegetable protein (TVP), used in the manufacture of meat and poultry analogs, by thermoplastic extrusion or steam texturization to impart structure and shape. In addition to protein, these soy protein ingredients contain other naturally occurring soy constituents, such as isoflavones, fiber, and saponins. The specific processing steps employed determine the extent of retention of such naturally occurring constituents in the final product.

Soy protein is also consumed in the diet as a component of traditional fermented and nonfermented soy foods such as tofu, tempeh, and miso, in addition to whole soybeans, soynuts, soy milk, soy yogurt, and soy cheese. These products contain variable amounts of soy protein and other naturally occurring soy constituents depending on the specific technologies used in their production.

Soy protein ingredients (ISP, SPC, and SF) and soy protein-containing foods may partially replace or be used in addition to animal or other vegetable protein sources in the human diet. Therefore, FDA has tentatively concluded that the substance satisfies the preliminary requirement of § 101.14(b)(3)(i).

3. The Substance Is Safe and Lawful

The petitioner stated that soy protein ingredients were in common use in food before January 1, 1958, and that they are generally recognized as safe (GRAS) by self-determination (Ref. 1). Because the fractionation procedures used to convert vegetable flours to vegetable protein isolates and concentrates were commonplace prior to 1958, the petitioner asserted that ISP and SPC can be defined as soy flour ''subject only to conventional processing as practiced prior to January 1, 1958.'' The petitioner alluded to statements that it attributed to FDA about the GRAS status of soy protein products. (In point of fact, however, in one document (35 FR 18530, December 5, 1970), FDA was restating a petitioner's grounds for its petition, and in the other document (43 FR 30472, July 14, 1978), FDA was stating a condition on the vegetable protein products to which the proposed regulation applied, and was not itself determining the safety or suitability of any product (43 FR 30472 at 30474 to 30475 (comment 10).) The petitioner also referred to unidentified statements by the U.S. Department of Agriculture, the Association of American Feed Control Officials, and the Codex Alimentarius that it asserted support for the GRAS status of soy protein products (Ref. 1).

The petition also addressed some concerns that have been raised about the potential risk of consuming soy products: Allergenicity, exposure to trypsin inhibitors, reduced bioavailability of minerals, and hormonal disturbances.

As is true for any protein entering the gastrointestinal tract, soy protein has the potential to elicit an allergic reaction. Food allergies most commonly develop in infants and young children. Although the use of heat or hot aqueous ethanol in the processing of soybeans destroys the immunochemical reactivity of most of the protein, a small number of infants fed soy formula experience allergic reactions to soy (Ref. 9). Such sensitization appears to be a manifestation of an immature digestive tract and is rarely seen in children more

than 4 years old or adults. Many children outgrow food allergies (Ref. 10) and soy and seafood allergies are among those likely to be outgrown, in contrast to allergies to milk, egg white, or peanuts.

Concerns have been raised in the past about exposure to trypsin inhibitors contained in soybeans because these compounds had been found to stimulate pancreatic hyperplasia and hypertrophy in animals (Ref. 11). These concerns have been allayed because heat treatment removes most of the activity of these proteases (Ref. 12). In addition, recent studies have questioned the applicability of the animal models, which differ from humans in the type of diet, sensitivity of the pancreas to trypsin inhibitors, and the anatomic sites of pancreatic cell proliferation (Refs. 12 through 15) and have found low rates of cancer in populations with dietary patterns that include soy foods (Ref. 16).

Soybeans contain phytic acid and dietary fiber, which have well documented effects on reducing the bioavailability of divalent minerals, and these components are retained in the protein fraction in variable amounts depending upon processing. In general, the bioavailability of minerals is lower from plant sources than animal sources, but soy has not been found to reduce the availability of minerals from other dietary sources consumed concurrently (Ref. 17). Data on the possible deleterious effects of soy, and particularly its phytate content, on mineral balance have been obtained mainly from studies of animal models; findings in humans are less consistent and suggest that although absorption may be impaired, overall mineral balance is not adversely affected (Refs. 13, 18, 19, 20).

Finally, the possibility of hormonal disturbances from the weakly estrogenic-antiestrogenic effects of soy isoflavones has been raised. For example, infertility was found in sheep that had consumed clover containing isoflavones (Ref. 21); however, studies of soy isoflavones in primates showed no effects on male or female reproductive tissue or ability (Refs. 22 through 24). Soy isoflavones have been hypothesized as a protective factor against breast cancer in populations that consume large amounts of soy protein (Ref. 25), and in one controlled human trial, a 45-mg/day dose of isoflavones lead to favorable changes in menstrual cycle length and hormone levels similar to those seen in women treated with tamoxifen (Ref. 26).

Based on the totality of the evidence and, in particular, its common use in food, the agency is not prepared, at this time, to take issue with the petitioner's view that the use of soy protein is safe and lawful as required in § 101.14(b)(3)(ii). Thus, FDA tentatively concludes that the petitioner has provided evidence that satisfies the requirement in § 101.14(b)(3)(ii) that use of soy protein at the levels necessary to justify a claim is safe and lawful.

III. Review of Scientific Evidence

A. Basis for Evaluating the Relationship Between Soy Protein and CHD

The review examined the relationship between soy protein and CHD by focusing on the effects of dietary intake of this substance on blood lipid levels and on the risk of developing CHD. In the 1991 lipids-CVD and dietary fiber-CVD health claim proposals, the agency set forth the basis for the relationship between dietary substances and CVD (56 FR 60727 at 60728 and 56 FR 60582 at 60583). In those documents, the agency stated that there are many risk factors that contribute to the development of CVD, and specifically CHD, one of the most serious forms of CVD and among the leading causes of death and disability. The agency also stated that there is general agreement that elevated blood cholesterol levels are one of the major ''modifiable'' risk factors in the development of CVD and, more specifically, CHD.

The Federal Government and others who have reviewed the matter have concluded that there is substantial epidemiologic evidence that high blood levels of total cholesterol and LDL-cholesterol are a cause of atherosclerosis (inadequate circulation of blood to the heart due to narrowing of the arteries) and represent major contributors to CHD (56 FR 60727 at 60728, 56 FR 60582 at 60583, Refs. 4 through 6). Factors that decrease total cholesterol and LDL-cholesterol will also tend to decrease the risk of CHD. High intakes of saturated fat and, to a lesser degree, of dietary cholesterol are associated with elevated blood total and LDL-cholesterol levels (56 FR 60727 at 60728). Thus, it is generally accepted that blood total cholesterol and LDL-cholesterol levels can influence the risk of developing CHD, and, therefore, that dietary factors affecting these blood cholesterol levels affect the risk of CHD (Refs. 4 through 6).

When considering the effect that the diet or components of the diet have on blood (or serum) lipids, it is also useful to consider the effect that these factors may have on blood levels of high density lipoprotein (HDL)-cholesterol. HDL-cholesterol appears to have a protective effect because it is involved in the regulation of cholesterol transport out of cells and to the liver, from which it is ultimately excreted (Refs. 4 and 8).

For these reasons, the agency based its evaluation of the relationship between consumption of soy protein and CHD primarily on changes in blood total and LDL-cholesterol resulting from dietary intervention with soy protein-containing products. A secondary consideration was that beneficial changes in total and LDL-cholesterol should not be accompanied by potentially adverse changes in HDL-cholesterol. This focus is consistent with that used by the agency in response to the 1990 amendments in deciding on the dietary saturated fat and cholesterol and CHD health claim, § 101.75 (56 FR 60727 and 58 FR 2739); the fruits, vegetables, and grain products and CHD claim, § 101.77 (56 FR 60582 and 58 FR 2552); and the soluble fiber from certain foods and CHD claim, § 101.81 (61 FR 296, 62 FR 3584, 62 FR 28234, and 63 FR 8119).

B. Review of Scientific Evidence

1. Evidence Considered in Reaching the Decision

The petitioner submitted scientific studies (Refs. 27 through 66) evaluating the relationship between soy protein in the diet and serum lipid levels in humans (Refs. 1 and 2). The studies submitted were conducted between 1976 and 1998. The petition included tables that summarized the outcome of the studies and a summary of the evidence. In the approach taken previously in the diet and CVD proposed rules, the agency began its review of scientific evidence in support of a health claim by considering those studies that were published since 1988, the date of publication of the ''Surgeon General's Report on Nutrition and Health,'' which is the most recent and comprehensive Federal review of the scientific evidence on dietary factors and CVD. In a brief discussion of the role of protein in coronary heart disease, the Surgeon General's report noted that studies of the substitution of soy protein and other vegetable proteins for animal protein in the diets of hyperlipidemic patients have shown a marked reduction in serum cholesterol levels but only a small change in persons with normal cholesterol levels (Ref. 4). Because of the brevity of this consideration of soy protein, the agency reviewed all of the studies on soy protein submitted by the petitioner, including those published prior to 1988.

The petition also presented some findings from studies that employed animal models and from in vitro

experiments. Human studies are weighted most heavily in the evaluation of evidence on a diet and disease relationship; animal model and in vitro studies can be considered as supporting evidence but cannot, in the absence of human studies, serve as the basis for establishing that a diet and disease relationship exists. Such studies may be useful in providing information on the mechanism of action of soy protein's effects on blood cholesterol levels.

2. Criteria for Selection of Human Studies

The criteria that the agency used to select the most pertinent studies were consistent with those that the agency used to evaluate the relationship between other substances and CHD. These criteria were that the studies: (1) Present data and adequate descriptions of the study design and methods; (2) be available in English; (3) include estimates of, or enough information to estimate, soy protein intakes; (4) include direct measurement of blood total cholesterol and other blood lipids related to CHD; and (5) be conducted in persons who represent the general U.S. population. In the case of (5), these persons can be considered to be adults with blood total cholesterol levels less than 300 mg/dL. Studies of special population groups, such as adults with very high serum cholesterol (mean greater than 300 mg/dL) and children with hypercholesterolemia, were considered relative to the nature of the support they provided for evidence of effect seen in studies of subjects more representative of the general U.S. population.

In a previous rulemaking (62 FR 28234 at 28238 and 63 FR 8103 at 8107), the agency concluded that hypercholesterolemic study populations are relevant to the general population because, based on data from the National Health and Nutrition Examination Surveys (NHANES) III, the prevalence of individuals with elevated blood cholesterol (i.e., 200 mg/dL or greater) is high, i.e., approximately 51 percent of adults (Ref. 7). The proportion of adults having moderately elevated blood cholesterol levels (i.e., between 200 and 239 mg/dL) was estimated to be approximately 31 percent, and the proportion of adults with high blood cholesterol levels (240 mg/dL or greater) was estimated to be approximately 20 percent (Ref. 7). It is also estimated that 52 million Americans 20 years of age and older would be candidates for dietary intervention to lower blood cholesterol (Ref. 7). As the leading cause of death in this country, CHD is a disease for which the general U.S. population is at risk. The risk of dying from CHD is related to serum cholesterol levels in a continuous and positive manner, increasing slowly for levels between 150 mg/dL and 200 mg/dL and more rapidly when the cholesterol level exceeds 200 mg/dL (Ref. 67). The public health policy elucidated by the National Cholesterol Education Program (NCEP), National Heart, Lung, and Blood Institute, is to extend the benefits of cholesterol lowering to the population as a whole by promoting adoption of eating patterns that can help lower the blood cholesterol levels of most Americans (Ref. 67). A dietary intervention that lowers blood cholesterol levels mainly or only in persons with high levels would, like an intervention that lowers cholesterol levels across the entire population range, cause a shift in the population distribution of blood cholesterol levels resulting in a decrease in the mean value for the blood cholesterol level in the general population (Ref. 67). The anticipated effect of such a shift would be to reduce the morbidity from CHD and to produce a continued or accelerated decline in the CHD mortality rate in the United States. Accordingly, in this proposal, the agency has reviewed and considered the evidence of effects of soy protein on serum lipids in hypercholesterolemic subjects.

In selecting human studies for review, the agency excluded studies that were published in abstract form because they lacked sufficient detail on study design and methodologies, and because they could not provide the primary data.

3. Criteria for Evaluating the Relationship Between Soy Protein and CHD

Well reasoned approaches for evaluating studies supporting diet/disease relationships are summarized in the comprehensive report ''Diet and Health'' issued by the National Academy of Sciences (Ref. 68) and ''The Guide to Clinical Preventive Services'' issued by the U.S. Preventive Services Task Force (Ref. 69). The criteria articulated in these documents provided a starting point for FDA's review of individual studies on the relationship between dietary factors and CHD in previous rulemakings: In the 1991 proposed rule on lipids and CVD (56 FR 60727), in the 1991 proposed rule on dietary fiber and CVD (56 FR 60582), in the January 1996 proposed rule on whole oats and CHD (61 FR 296), and in the May 22, 1997, proposed rule on soluble fiber from psyllium and CHD (62 FR 28234).

The criteria that the agency used in evaluating the studies for this rulemaking include: (1) Reliability and accuracy of the methods used in nutrient intake analysis, including measurements of soy protein intake; (2) estimates of intake of saturated fat and cholesterol; (3) available information on the soy protein test products and control foods; (4) measurement of study endpoints (i.e., measurement of blood lipid levels); and (5) general study design characteristics.

The general study design characteristics for which the agency looked included randomization of subjects, appropriateness of controls, selection criteria for subjects, attrition rates (including reasons for attrition), potential for misclassification of individuals with regard to dietary intakes, presence of recall bias and interviewer bias, recognition and control of confounding factors (for example, monitoring body weight and control of weight loss), appropriateness of statistical tests and comparisons, and statistical power of the studies. The agency considered whether the intervention studies that it evaluated had been of long enough duration, greater than or equal to 3 weeks duration, to ensure reasonable stabilization of blood lipids.

C. Review of Human Studies

FDA conducted a comprehensive review of 41 of 43 human intervention studies submitted in the petition and reported in 38 references by the petitioner (Refs. 27 through 64). The two studies FDA excluded from consideration at the outset (Refs. 32 and 52) were of infants. Of the studies reviewed, 27 met the aforementioned criteria for selection (Refs. 27, 28, 29, 30 (1 trial), 31, 33, 34, 35, 36, 37, 40 (2 trials), 42 and 45 (1 trial), 43, 44, 46, 49, 51, 53, 54, 55, 56, 58, 59, 60, 63, and 64). Of these, the agency gave particular weight to 14 trials (Refs. 27, 28, 30 (1 trial), 31, 36, 37 (1 trial), 40 (2 trials), 44, 49, 51, 54, 58, and 59) that included subjects representative of the general U.S. population and that were well controlled, reported intakes of saturated fat and cholesterol, and avoided problems associated with small sample size, lack of a placebo, and other design problems. These studies are summarized in Table 1 at the end of this document and discussed in section III.C.1 of this document. Three additional similar trials that were included in the review but accorded less weight because of issues concerning the populations studied and diets fed (Refs. 29, 43, and 53) are also summarized in Table 1 of this document and discussed in section III.C.1 of this document. Seven trials in adults (Refs. 33, 35, 46,

55, 56, 60, and 64) and three trials in children (Refs. 34, 42 and 45 (1 trial), and 63) with type II or familial hypercholesterolemia are summarized in Table 2 at the end of this document and discussed in section III.C.2 of this document. The fourteen remaining intervention trials (Refs. 30 (1 trial), 37 (1 trail), 38, 39 (2 trials), 41, 47, 48, 50 (2 trials), 57, 61, and 62 (2 trials)) failed to meet the inclusion criteria because of small sample size, inadequate period of intervention, inadequate characterization of the soy protein tested, inadequate information on dietary intake, or lack of data on outcome variables. The results of one epidemiological study (Ref. 65) and a meta-analysis (Ref. 66) that included a number of the soy protein studies submitted in the petition are discussed in sections III.C.3 and III.C.4, respectively, of this document.

1. Studies of Adult Subjects Representative of the General U.S. Population (Serum Cholesterol <300 mg/dL)

The agency began its consideration of the data with the 14 well controlled and representative studies identified previously (Refs. 27, 28, 30 (1 trial), 31, 36, 37 (1 trial), 40 (2 trials), 44, 49, 51, 54, 58, and 59). Several of these studies examined the interaction of protein and other components of soy protein sources hypothesized to have an impact on lipid-lowering effects (i.e., isoflavones, dietary fiber, and soy lipids) (Refs. 31, 28, 27, 51, and 44). Findings with respect to soy protein are described in this section, while findings regarding the specific influence of soy isoflavones (Refs. 31 and 28) are discussed in more detail in section III.C.5 of this document.

In hypercholesterolemic subjects, Crouse et al. (Ref. 31, documented in Ref. 1 with corrections noted in Ref. 2) found that 25 grams (g) of soy protein from ISP containing 2.5 mg total aglycone isoflavones/g protein lowered total ($p<0.05$) and LDL-cholesterol levels ($p<0.05$) by 4 and 6 percent, respectively, while HDL-cholesterol was not altered. Furthermore, in subjects with LDL-cholesterol levels in the top half of the study population, serum total and LDL-cholesterol were reduced by 9 percent ($p<0.03$) and 12 percent ($p<0.03$), respectively, by the ISP with 2.5 mg total aglycone isoflavones/g protein, and by 8 percent ($p<0.03$) and 9 percent ($p<0.03$), respectively, by the ISP with 1.6 mg total aglycone isoflavones/g protein. HDL-cholesterol concentrations were unchanged. These results indicate that soy protein, in a diet low in saturated fat and cholesterol, can exert hypocholesterolemic effects but suggest these effects may be modulated by the presence of isoflavones.

In hypercholesterolemic, postmenopausal women, Baum et al. (Ref. 28) also investigated the impact of soy protein as ISP containing different levels of isoflavones. Adjusted mean differences in the change from baseline for total serum cholesterol level did not differ in the two soy groups and the control group. However, there was a statistically significant reduction of 8 to 9 percent in non-HDL (LDL plus very low density lipoprotein (VLDL)) cholesterol in both of the ISP treatment groups ($p<0.05$) compared to the control group. HDL-cholesterol was also significantly increased ($p<0.05$) in both soy groups compared to the control. The level of isoflavones did not affect any of the blood lipid levels measured. This study also indicates the ability of soy protein provided in a diet low in saturated fat and cholesterol to reduce LDL-cholesterol.

Two studies that examined the effect of soy protein in hypercholesterolemic adults consuming low fat diets also evaluated whether soy cotyledon fiber had additional lipid-lowering effects. Bakhit et al. (Ref. 27) used 25 g protein and 20 g dietary fiber as treatment levels while Potter et al. (Ref. 51) used 50 g protein and 20 g dietary fiber. Soy protein was provided as ISP (Refs. 27 and 51) and SF (Ref. 51) incorporated into baked products.

Bakhit et al. (Ref. 27) studied subjects who had initially been screened for eligibility based on plasma total cholesterol concentrations greater than 220 mg/dL before starting the study. During the baseline dietary period, plasma total cholesterol decreased to levels below 220 mg/dL in 10 of the subjects; these subjects did not have any further decrease in total or LDL-cholesterol with any of the experimental diets. The subjects whose cholesterol remained greater than the 220 mg/dL intent-to-treat level did show a statistically significant decrease from post-baseline dietary levels for total cholesterol, but not for LDL-cholesterol, after consuming ISP. In the subset analysis, Bakhit et al. (Ref. 27) found a statistically significant decrease in total cholesterol of 7 percent ($p<0.05$) from post-stabilization levels with ingestion of ISP. Addition of soy cotyledon fiber to the ISP diet resulted in a statistically significant decrease ($p<0.05$) of 8 percent in total cholesterol. Ingestion of the casein plus cellulose control diet produced a nonsignificant decrease ($p>0.05$) in total cholesterol of 3 percent. Differences in LDL- and HDL-cholesterol from baseline or control after the two soy diets were not statistically significant. In the subset analysis, the additional effect of soy fiber on blood cholesterol levels was not significant when evaluated by analysis of covariance ($p=0.04$ for protein effects; $p=0.07$ for fiber effects). This study supports a conclusion that the protein and not the fiber component of the soybean is largely responsible for effects on blood lipids.

Potter et al. (Ref. 51) reported a statistically significant ($p<0.05$) decrease in plasma total cholesterol from baseline of 8 percent with ingestion of diets containing ISP whether soy cotyledon fiber or cellulose was also consumed. The 8-percent decrease observed in LDL-cholesterol from baseline was statistically significant only when the ISP diet also contained soy cotyledon fiber ($p<0.05$). Total and LDL-cholesterol were also significantly ($p<0.01$) lower with the ISP diets compared to the nonfat dry milk-cellulose control diet. No statistically significant changes in HDL-cholesterol were observed with any of the soy protein diets. Changes from baseline were not statistically significant for any of the blood lipids when the diet providing soy protein as SF was consumed. However, the difference in total cholesterol observed after ingestion of SF was 19 mg/dL lower than that on the control diet of nonfat dry milk and cellulose ($p<0.01$). These findings suggest that the principal dietary component responsible for the lipid-lowering observed in this study is the soy protein fraction, and that soy fiber may have an incremental effect.

Kurowska et al. (Ref. 44) tested the effects of soy protein and soy oil in hypercholesterolemic subjects by adding combinations of ''milk'' and desserts to provide a total of 31 g protein from either cow's milk or soy milk and 16 g fat from either cow's milk, soybean oil, or whole soybean soy milk. The three dietary treatments were cow's milk (2-percent fat), skim cow's milk (0-percent fat) plus soy oil (16 g), or soybean milk. No statistically significant changes from baseline in total cholesterol were observed in response to any of the dietary treatments. The 4-percent decline in LDL-cholesterol observed with the soybean milk diet was not statistically significant. HDL-cholesterol was increased 7 percent from baseline ($p=0.04$) with the whole soybean milk treatment. In the subjects with the highest initial LDL-cholesterol level and LDL/HDL-cholesterol ratio, LDL-cholesterol was reduced by 11 percent by the soybean milk diet.

Five earlier studies included in Table 1 reported on effects of soy protein in hypercholesterolemic subjects.

In hypercholesterolemic subjects, Goldberg et al. (Ref. 37) examined the effects of ISP (99 g of soy protein) incorporated as a meat analog or formulated in beverage compared to a control animal protein diet consisting of analogous meat products and nonfat dry milk. Both diets resulted in statistically significant reductions in serum total and LDL-cholesterol levels. With the soy protein diet, total cholesterol was decreased by 15 percent ($p<0.001$) and LDL-cholesterol was decreased by 17 percent ($p<0.001$) from baseline values. Total cholesterol was 8 mg/dL lower ($p<0.005$), and LDL-cholesterol was 10 mg/dL lower ($p<0.05$), at the end of the dietary period when soy protein was ingested as compared to the animal protein diet. Both the change in HDL-cholesterol from the baseline and the difference in HDL-cholesterol between the soy and control diets were small and not statistically significant.

Mercer et al. (Ref. 49) tested the effects of approximately 17 g of soy protein from ISP as a replacement for 2-percent fat cow's milk in subjects with mild to moderate hypercholesterolemia. Total cholesterol levels were not significantly different ($p>0.05$) on the two diets. However, among the subjects whose baseline total cholesterol was above the 90th percentile, the soy protein diet resulted in a decrease from baseline in mean total cholesterol of 4 percent and a level 9 percent lower (16 mg/dL; $p<0.05$) than the level at the end of the cow's milk period. There were no statistically significant differences in LDL-cholesterol and HDL-cholesterol between ISP and cow's milk diets either for all subjects or for the subset of subjects with the highest initial total cholesterol levels.

Holmes et al. (Ref. 40) conducted two trials with hypercholesterolemic subjects testing SF as a texturized vegetable protein product formulated with egg yolk, beef tallow, and cottonseed oil to create an analog for lean ground beef. An average of 27 g of soy protein was consumed in the partially substituted diet in the first trial and 62 g was consumed in the completely substituted diet in the second trial. In trial 1, statistically significant changes in total cholesterol ($p<0.02$) and LDL-cholesterol ($p<0.05$) occurred during the initial stabilization period when the control diet was consumed; no further changes occurred after the second period during which the partially substituted soy diet was consumed. In trial 2, both diets significantly lowered mean total cholesterol during the first dietary sequence ($p<0.05$), the animal protein diet by 18 percent and the soy diet by 19 percent. Crossing over the diets had no further effect. LDL-cholesterol levels were not reduced by either diet. HDL-cholesterol levels were not significantly affected by diet in either trial. The two trials were unique in the source of soy protein and in including subjects with type IV hyperlipidemia.

Shorey et al. (Ref. 54) examined the effects of 57 g of soy protein (mean intake) consumed as ISP incorporated both into meat analogs and a soy-based beverage in hypercholesterolemic young men. A statistically significant ($p=0.027$) decrease from baseline total cholesterol of 7 percent was noted in the group consuming the soy protein diet; however, these values were 6 mg/dL higher than change from baseline values obtained from the control group. HDL-cholesterol also significantly ($p=0.001$) decreased from baseline values by 15 percent. LDL-cholesterol was not measured in this study. Although the two diets were well matched for saturated fat and cholesterol, interpretation of these findings is complicated by the fact that body weight was significantly ($p<0.004$) decreased in both groups of subjects. Subjects who showed a significant hypocholesterolemic response on either diet were those who substantially reduced their customary protein and fat intakes on the experimental diets. In contrast to other studies, subjects in this study with lower baseline values experienced more pronounced reductions in total cholesterol level.

Four additional well-controlled studies included in Table 1 of this document examined the effects of soy protein in normocholesterolemic subjects.

The study of Carroll et al. (Ref. 30) compared ISP (44 g soy protein estimated) incorporated into foods and a soy-based beverage to a mixed protein/animal-based diet in healthy young women. Plasma total cholesterol was significantly ($p<0.05$) lower, by 10 mg/dL, when the soy protein diet was consumed as compared with the mixed protein diet. Neither LDL-cholesterol nor HDL-cholesterol was measured.

Giovannetti et al. (Ref. 36) examined the effects of ISP (66 to 80 g of soy protein depending on energy intake) incorporated as meat and dairy analogs in healthy young adult women in both high- and low-fat diets. On the high-fat diet, serum total cholesterol was 4 mg/dL lower, LDL-cholesterol was 6 mg/dL lower, and HDL-cholesterol was 3 mg/dL lower after ingestion of the soy protein than after ingestion of the mixed protein control. None of the changes in blood lipids reached statistical significance. On the low-fat diet, serum total cholesterol was 1 mg/dL higher, LDL-cholesterol was 5 mg/dL lower, and HDL-cholesterol was 2 mg/dL higher after soy protein than after the mixed protein control; these differences were not statistically significant. The magnitude of reduction in serum total cholesterol with soy protein was similar on the high-fat and low-fat diets, 10 percent and 9 percent, respectively. Substitution of soy protein caused reductions in LDL-cholesterol levels during the high-fat diet in 11 of 12 subjects and during the low-fat diet in 9 of 12 subjects.

Van Raaij et al. (Ref. 58) tested the effects of ISP in young normocholesterolemic men and women consuming three diets that differed in protein composition with 65 percent of the total protein replaced by either soy protein (54 g), or casein, or an approximately 2:1 mixture of casein (36 g):soy (17 g). In the group consuming the soy protein diet, total serum cholesterol and LDL-cholesterol were decreased (-2 percent and -8 percent, respectively) and HDL-cholesterol increased (+10 percent) compared to values at the end of the lead-in period. The changes in both LDL-cholesterol and HDL-cholesterol were statistically significant ($p<0.05$). In addition, decreases in LDL-cholesterol were significantly ($p<0.05$) greater with the soy protein diet compared to changes with the casein diet. Although weight loss did occur among subjects consuming both the soy protein diet ($n=9$) and the casein diet ($n=6$), when data from the subset without a weight loss of more than 2 kilograms (kg) were analyzed separately, the same effects of soy protein ingestion on blood lipid-lowering were observed. The lipid changes in the group that remained on the 2:1 casein:soy diet were not statistically significantly different from the casein group, nor were changes from the end of the stabilization period significant in this group.

In a trial with both normocholesterolemic and hypercholesterolemic subjects, Van Raaij et al. (Ref. 59) tested both ISP and SPC (each providing an average of 55 g of soy protein) compared to a casein control. Serum total cholesterol was decreased from baseline by 4 percent and LDL-cholesterol was decreased by 3 percent on the ISP diet. These changes were significantly different from those on the SPC diet ($p<0.05$) but not significantly different from those on the casein diet. HDL-cholesterol showed a slight but statistically significant

increase of 2 percent from baseline on the ISP diet, a change that was also significantly different from that on the casein diet. When SPC was used as the protein source, total cholesterol was not altered, LDL-cholesterol was increased by 6 percent, and HDL-cholesterol decreased by 3 percent compared to baseline. None of these changes in blood lipids from baseline or differences between the casein and SPC diets was statistically significant. Interpretation of this study is complicated by differential weight loss on the experimental diets (weight loss was greatest in the casein group) and differential fiber intake.

Three additional studies (Refs. 29, 43, and 53), in which interpretation is complicated by design issues such as choice of subjects, concerns about weight loss, or uncertainties about other components in diets, are also summarized in Table 1 of this document and discussed as follows.

Bosello et al. (Ref. 29) and Jenkins et al. (Ref. 43) both studied the hypocholesterolemic effects of soy protein versus casein in the context of hypocaloric diets fed to obese persons to achieve significant weight reduction. In Bosello et al. (Ref. 29), obese subjects (>150 percent of ideal body weight) received 375 kilocalorie (kcal)/day initially, followed by an 800 kcal/day diet. During both phases, the 375 kcal portion was provided by commercial textured protein products that delivered either 27 g protein from casein or 27 g protein from soy protein (type of soy protein not given). During the second phase, the 375 kcal/day was ''integrated'' with an extra 425 kcal/day from conventional foods. Mean weight losses for the soy and casein groups were 17 and 16 kg, respectively. Total cholesterol and LDL-cholesterol in the soy group were both 16 percent lower compared to baseline ($p<0.01$). Compared to the casein group, total cholesterol was 20 mg/dL lower ($p<0.01$) and LDL-cholesterol was 16 mg/dL lower ($p<0.01$). HDL-cholesterol was decreased in both groups at the end of the study; however, only in the casein group was the difference statistically significant ($p<0.01$). Additionally, the decrease in HDL-cholesterol in the casein group was significantly ($p<0.01$) greater than that observed in the soy protein group.

Jenkins et al. (Ref. 43) examined the effects of soy protein ingestion on serum cholesterol in obese women who were also consuming a hypocaloric diet for weight reduction. The three treatments were: A control, hypocaloric diet of 1,000 total kcal consumed as conventional foods; the same diet with two meals per day replaced by a soy protein (18.4 g provided as ISP) liquid formula preparation; or the same diet with two meals per day replaced by a milk protein (17.6 g as milk protein isolate and nonfat dry milk) liquid formula. An average 2.5 kg weight loss per month occurred during the study ($p<0.05$) across diet treatments. Statistically significant decreases from baseline in total cholesterol of 10 percent ($p<0.05$) and in LDL-cholesterol of 17 percent ($p<0.05$) occurred only during the period when the soy protein formula was ingested. Changes in HDL-cholesterol were not statistically significant. These effects of soy protein were independent of the order the soy diet was consumed relative to the conventional hypocaloric diet. The levels of total and LDL-cholesterol achieved with ingestion of soy protein were, respectively, 10 mg/dL and 8 mg/dL lower with the soy protein diet as compared with the casein diet. Neither the conventional hypocaloric diet nor the casein formula hypocaloric diet resulted in statistically significant decreases in total or LDL-cholesterol despite weight loss. Calculations of the expected decline in serum total cholesterol based on changes in weight, dietary cholesterol, and saturated and polyunsaturated fat accurately predicted the observed changes in both the hypocaloric diet and milk formula groups, but significantly underestimated the decrease observed in the soy formula group.

Sacks et al. (Ref. 53) studied the effects of 27 g of protein consumed daily as ISP or casein incorporated into muffins and oatmeal in adults who were strict vegetarians. Not unexpectedly, given the very low baseline lipid concentrations and very low dietary fat and cholesterol intake, no statistically significant changes or differences in total cholesterol, LDL-cholesterol or HDL-cholesterol were observed from consumption of either soy protein or casein.

a. *Summary—Hypercholesterolemic subjects consuming diets low in saturated fat and cholesterol.* In five (Refs. 31, 28, 27, 51, and 44) of seven (Refs. 31, 28, 27, 51, 44, and 40 (2 trials)) well-controlled studies of hypercholesterolemic subjects consuming low saturated fat and low cholesterol diets, soy protein intake was associated with significant decreases in total and/or LDL-cholesterol levels. Crouse et al. (Ref. 31, documented in Ref. 1 with corrections noted in Ref. 2) found that soy protein from ISP containing 2.5 mg total aglycone isoflavones/g protein statistically significantly lowered total ($p<0.05$) and LDL-cholesterol levels ($p<0.05$), by 4 and 6 percent, respectively, while HDL-cholesterol was not altered. In a subset of subjects with LDL-cholesterol levels in the top half of the study population, serum total and LDL-cholesterol were reduced by 9 percent ($p<0.03$) and 12 percent ($p<0.03$), respectively, by the ISP with 2.5 mg total aglycone isoflavones/g protein, and by 8 percent ($p<0.03$) and 9 percent ($p<0.03$), respectively, by the ISP with 1.6 mg total aglycone isoflavones/g protein. Baum et al. (Ref. 28) found that the adjusted mean difference in total serum cholesterol level was not significantly ($p>0.05$) different in the two groups consuming soy as ISP and the control group. However, there was a statistically significant reduction of 8 to 9 percent in non-HDL (LDL plus VLDL) cholesterol in both of the ISP treatment groups ($p=0.04$) compared to the control group.

Bakhit et al. (Ref. 27) found, in a subset of subjects whose cholesterol remained greater than the 220 mg/dL intent-to-treat level after run-in with the baseline diet, a statistically significant decrease in total cholesterol of 7 percent ($p<0.05$) from post-stabilization levels with ingestion of ISP; addition of soy cotyledon fiber to the ISP diet resulted in a significant decrease ($p<0.05$) of 8 percent in total cholesterol. Levels of LDL-cholesterol were not statistically significantly affected by either soy diet. Potter et al. (Ref. 51) reported a statistically significant decrease ($p<0.05$) from baseline in total plasma cholesterol of 8 percent with ingestion of diets containing ISP whether soy cotyledon fiber or cellulose was also consumed. The 8-percent decrease in LDL-cholesterol from baseline was statistically significant only when the ISP diet also contained soy cotyledon fiber ($p<0.05$). Total and LDL-cholesterol were also significantly lower ($p<0.01$) with the ISP diets compared to the nonfat dry milk-cellulose diet. Changes from baseline were not statistically significant for any of the blood lipids when the diet providing soy protein as SF was consumed. However, the difference in total cholesterol observed after ingestion of SF was 19 mg/dL lower than that on the control diet of nonfat dry milk and cellulose ($p<0.01$).

With diets providing either cow's milk (2-percent fat), or skim cow's milk (0-percent fat) plus soy oil (16 g), or soybean milk, Kurowska et al. (Ref. 44) found no statistically significant changes from baseline in total cholesterol and LDL-cholesterol in response to any of the dietary treatments. In the subjects with the highest initial LDL-cholesterol levels and LDL/HDL-cholesterol ratios, LDL-

cholesterol was reduced by 11 percent by the soybean milk diet. Holmes et al. (Ref. 40) conducted two trials testing SF as a texturized vegetable protein product, with averages of 27 and 62 g of soy protein consumed, respectively, in the first and the second trial. In trial 1, statistically significant changes in total and LDL-cholesterol occurred during the stabilization period when the control diet was consumed; no further changes occurred after the second dietary period during which the partially substituted soy diet was consumed. In trial 2, both diets resulted in a statistically significant lowering of total cholesterol during the first dietary sequence, the animal protein diet by 18 percent and the soy diet by 19 percent. Crossing over the diets had no further effect. LDL-cholesterol levels were not reduced by either diet. These studies were unique in the source of soy protein used and in including subjects with type IV hyperlipidemia.

Levels of HDL-cholesterol were also measured in each of these seven studies and were found either to be unchanged (Refs. 31, 27, 51, and 40 (2 trials)) or to show a slight but statistically significant increase (Refs. 28 and 44) in response to consumption of diets containing soy protein.

Levels of soy protein as ISP found to be effective in lowering total and LDL-cholesterol levels ranged in these studies from 25 to 50 g (Refs. 31, 28, 27, and 51). As whole soybean milk, 31 g of soy protein lowered LDL-cholesterol only in the subset of subjects with the highest initial LDL-cholesterol levels and LDL/HDL-cholesterol levels (Ref. 44). Diets providing 50 g of soy protein as SF did not cause significant changes from baseline for any of the blood lipids, but the decrease in total cholesterol observed after ingestion of SF was significantly greater than that on the control diet of nonfat dry milk and cellulose (Ref. 51). Diets providing 27 g of soy protein as SF in a textured product had no significant effects on blood lipid levels compared to a control diet, and a higher level (62 g) significantly lowered total cholesterol only in the experimental group fed the soy protein diet first (Ref. 40).

b. *Summary—Hypercholesterolemic subjects consuming ''usual'' diets.* Three studies reported on effects of soy protein in hypercholesterolemic subjects consuming ''usual'' diets that were generally high in total fat, saturated fat, and cholesterol (Refs. 37, 49, and 54). Goldberg et al. (Ref. 37) found, on the soy protein diet (with 99 g of soy protein as ISP), statistically significant decreases from baseline of 15 percent in total cholesterol and 17 percent in LDL-cholesterol. Total cholesterol was 8 mg/dL lower ($p<0.005$), and LDL-cholesterol was 10 mg/dL lower ($p<0.05$), at the end of the dietary period when soy protein was ingested as compared to the animal protein diet. Mercer et al. (Ref. 49) found that a diet with approximately 17 g of soy protein from ISP did not produce changes in serum cholesterol that were significantly different from those of a cow's milk control diet. Among subjects whose baseline total cholesterol was above the 90th percentile, Mercer et al. (Ref. 49) found that the soy protein diet resulted in a decrease from baseline in mean total cholesterol of 4 percent and a level 9 percent lower (16 mg/dL; $p<0.05$) than the level at the end of the cow's milk control period. LDL-cholesterol did not differ significantly between ISP and cow's milk diets for all subjects or for the subset of subjects with the highest initial total cholesterol levels.

Shorey et al. (Ref. 54) found diets with 57 g of soy protein as ISP was associated with a statistically significant decrease from baseline in total cholesterol of 7 percent ($p=0.027$); however, these values were 6 mg/dL higher than change from baseline values obtained from the control group. LDL-cholesterol was not measured in this study. Although the two diets were well matched for saturated fat and cholesterol, interpretation of these findings is complicated by the fact that body weight was significantly decreased in both groups of subjects ($p<0.004$). Subjects who showed a significant hypocholesterolemic response on either diet were those who substantially reduced their customary protein and fat intakes on the experimental diets. In contrast to other studies, subjects in this study with lower baseline values experienced more pronounced reductions in total cholesterol level.

HDL-cholesterol was also measured in these three studies. Changes were small and not statistically significant in two studies (Refs. 37 and 49), but HDL-cholesterol was significantly decreased from baseline values by 15 percent in one study (Ref. 54). (This latter study had a number of anomalous results.)

Each of these three studies fed soy protein in experimental diets as ISP (Refs. 37, 49, and 54). With a diet containing a very high level (99 g) of soy protein from this source (Ref. 37), statistically significant differences in both total and LDL-cholesterol were reported. Results were less consistent with a relatively low level of soy protein (17 g) (Ref. 49). An intermediate level of soy protein (57 g) was found to be ineffective in lowering total cholesterol in the study of Shorey et al. (Ref. 54).

c. *Summary—Normocholesterolemic subjects.* Five studies examined the effects of soy protein in normocholesterolemic subjects (Refs. 30, 36, 58, 59, and 53). The study of Carroll et al. (Ref. 30) found plasma total cholesterol was significantly lower (-10 mg/dL) when a soy protein diet (low in saturated fat and cholesterol and providing an estimated 44 g soy protein as ISP) was consumed as compared with a mixed protein control diet ($p<0.05$). LDL-cholesterol was not measured. Giovannetti et al. (Ref. 36) examined the effects of soy protein as ISP (66 to 80 g of soy protein depending on energy intake) in both high- and low-fat diets. Changes in total and LDL-cholesterol with the soy protein diets were not statistically significantly different from changes with the corresponding control diets, regardless of fat content. The magnitude of reduction in serum total cholesterol with soy protein was similar on the high-fat and low-fat diets, 10 percent and 9 percent, respectively. Substitution of soy protein caused reductions in LDL-cholesterol levels during the high-fat diet in 11 of 12 subjects and during the low-fat diet in 9 of 12 subjects.

Van Raaij et al. (Ref. 58) tested the effects of ISP using three diets high in total fat, saturated fat, and cholesterol that differed in protein composition with 65 percent of the total protein comprising either soy protein (54 g), or casein, or an approximately 2:1 mixture of casein (36 g):soy (17 g). In the group consuming the soy protein diet, the decrease in total serum cholesterol (-2 percent) was not statistically significant, but the decrease in LDL-cholesterol (-8 percent) was statistically significant ($p<0.05$). In addition, decreases in LDL-cholesterol were significantly greater with the soy protein diet compared to changes with the casein diet ($p<0.05$).

In a trial with both normocholesterolemic and moderately hypercholesterolemic subjects, Van Raaij et al. (Ref. 59) tested both ISP and SPC (each providing an average of 55 g of soy protein) compared to a casein control in diets high in total fat, saturated fat, and cholesterol. Serum total cholesterol was decreased from baseline by 4 percent and LDL-cholesterol was decreased by 3 percent on the ISP diet. These changes were statistically significantly different from those on the SPC diet ($p<0.05$) but not significantly different from those on the casein diet. When SPC was used as the protein source, total cholesterol was not altered and LDL-cholesterol was increased by 6 percent compared to

baseline. None of these changes in blood lipids from baseline or differences between the casein and SPC diets was statistically significant. Interpretation of this study is complicated by differential weight loss on the experimental diets (weight loss was greatest in the casein group) and differential fiber intake.

Sacks et al. (Ref. 53) studied the effects of 27 g of protein consumed daily as ISP or casein incorporated into muffins and oatmeal, in diets very low in saturated fat and cholesterol in adults who were strict vegetarians. Not unexpectedly, given the very low baseline lipid concentrations and very low dietary fat and cholesterol intake, no statistically significant changes or differences in total cholesterol or LDL-cholesterol or HDL-cholesterol were observed from consumption of either soy protein or casein.

HDL-cholesterol was measured in four of these studies, with statistically significant increases associated with soy protein intake found in two (Refs. 58 and 59) and no statistically significant changes in two (Refs. 36 and 53).

Effects of soy protein on total and LDL-cholesterol were less consistent in normocholesterolemic subjects than in moderately hypercholesterolemic subjects. As ISP, 44 g of soy protein was effective in statistically significantly lowering total cholesterol in one study (Ref. 30), and 54 g statistically significantly lowered LDL-cholesterol in one study (Ref. 58). With very low initial blood lipid levels, the impact of dietary changes appears to be lessened.

d. *Summary—Subjects consuming hypocaloric diets.* Bosello et al. (Ref. 29) and Jenkins et al. (Ref. 43) both studied the hypocholesterolemic effects of soy protein versus casein in the context of hypocaloric diets fed to obese persons to achieve significant weight reduction. In Bosello et al. (Ref. 29), total cholesterol and LDL-cholesterol in the soy group (which consumed 27 g of soy protein) were both 16 percent lower compared to baseline ($p<0.01$). Compared to the casein control group, total cholesterol was 20 mg/dL lower ($p<0.01$) and LDL-cholesterol was 16 mg/dL lower ($p<0.01$) in the soy protein group. Jenkins et al. (Ref. 43) found that statistically significant decreases from baseline in total cholesterol of 10 percent ($p<0.05$) and in LDL-cholesterol of 17 percent ($p<0.05$) occurred only during the period when the soy protein formula (which provided 17 g of soy protein) was ingested. The levels of total and LDL-cholesterol achieved with ingestion of soy protein were, respectively, 10 mg/dL and 8 mg/dL lower with the soy protein diet compared with casein diet. Neither the conventional hypocaloric diet nor the casein formula hypocaloric diet resulted in statistically significant decreases in total or LDL-cholesterol despite weight loss.

HDL-cholesterol was decreased in both groups at the end of the first study (Ref. 29); however, only the casein group's values were significantly ($p<0.01$) different from baseline. Additionally, the decrease in HDL-cholesterol in the casein group was significantly($p<0.01$) greater than that observed in the soy protein group. In the second study (Ref. 43), HDL-cholesterol levels were not significantly affected by dietary treatment.

These two studies (Refs. 29 and 43) demonstrated decreases in both total and LDL-cholesterol levels during hypocaloric diets that provided relatively low amounts (27 and 17 g, respectively) of soy protein.

2. Studies of Subjects with Type II and Familial Hypercholesterolemia (Mean Total Cholesterol Level>300 mg/dL)

Ten studies (Refs. 33, 35, 46, 55, 56, 60, 64, 34, 42 and 45 (1 trial), and 63) of subjects with severe (type II or familial) hypercholesterolemia (mean total cholesterol level>300 mg/dL) are summarized in Table 2 of this document and discussed in section III. C.2 of this document. Seven report results in adults (Refs. 33, 35, 46, 55, 56, 60, and 64) and three in children (Refs. 34, 42 and 45 (1 trial), and 63).

a. *Studies in adults.* Sirtori et al. (Ref. 55) reported a decrease of 21 percent in both total ($p<0.001$) and LDL-cholesterol ($p<0.01$) with soy protein consumption in adults with type II hyperlipoproteinemia. Total intake of soy protein, as a textured protein isolate, was not given but was approximately 13 percent of kcal or 60 g. The order in which the soy protein diet was consumed did not affect the results and the changes in total plasma cholesterol level far exceeded those expected based on the small differences in ratio of polyunsaturated to saturated fat and cholesterol content of the diets. When the control diet was fed first, statistically significant changes in total and LDL-cholesterol were not observed; when it was fed second, total cholesterol increased statistically significantly. These investigators also reported that addition of 500 mg cholesterol in a small, similar study showed that level of dietary cholesterol did not modify the cholesterol-lowering effect of soy protein observed.

Descovich et al. (Ref. 33) examined the effects of soy protein replacing animal protein in adults with stable type IIa and IIb hypercholesterolemia. Subjects consumed an average of 47 g of soy protein in the form of texturized soy protein (from SF) mixed into main dishes. During the baseline control period with a lipid-lowering diet, plasma total cholesterol decreased 3 percent from baseline levels. When soy protein was substituted for animal protein in the second dietary period, total cholesterol decreased by 24 percent ($p<0.001$) at the end of the experimental period. All of the subjects demonstrated decreases in total cholesterol of at least 10 percent. Upon returning to the control diet, plasma total cholesterol increased 7 percent in men and 9 percent in women. LDL-cholesterol also showed a statistically significant decrease, by 31 percent from baseline levels ($p<0.001$), while HDL-cholesterol remained stable over the course of the soy protein diet (+0.4 mg/dL for men and +1.0 mg/dL for women).

Wolfe et al. (Ref. 64) tested the effects of ingesting 47 g of soy protein in the form of ISP incorporated into main dishes and a beverage, while animal proteins were incorporated into similar main dishes and cow's milk was consumed during the mixed protein control period. Baseline lipid concentrations were not given; however, mean total cholesterol concentrations were 280 mg/dL after the soy protein treatment and 321 mg/dL after the control treatment. Thus, compared with the control period, serum total cholesterol was 41 mg/dL lower with ingestion of soy protein ($p<0.05$) and LDL-cholesterol was 43 mg/dL lower ($p<0.05$). HDL-cholesterol was similar at the end of the soy protein and control dietary periods.

Sirtori et al. (Ref. 56) conducted a trial that examined the effects of complete and partial substitution of soy protein as SF (60 g or 30 g of soy protein), in a lecithinated textured vegetable protein, for animal protein in adults with type IIa hyperlipoproteinemia. Plasma cholesterol levels were not altered during the first control diet period. Total plasma cholesterol levels were significantly ($p<0.01$) reduced in both periods of soy protein administration, by 18.6 percent when 60 g were consumed and by 13.2 percent when 30 g were consumed. Serum cholesterol values returned almost completely to baseline during the second control period. Changes in LDL-cholesterol levels were superimposable to those of total cholesterol. HDL-cholesterol levels tended to increase during the two soy periods and decline to baseline levels during the second control period, but these differences were not statistically significant.

Verillo et al. (Ref. 60) compared the effects of substituting 31 g of soy protein

as SF for animal protein versus the addition of 31 g of soy protein as SF to animal protein in adults with stable type II hypercholesterolemia. Slight, nonsignificant decreases in total and LDL-cholesterol levels were reported during the initial control period. Among subjects who consumed the soy-substituted diet, serum total cholesterol declined significantly ($p<0.01$) from the end of the baseline diet by 35 percent and 23 percent in type IIa and type IIb patients, respectively. LDL-cholesterol declined significantly ($p<0.01$) from the end of the baseline diet by 44 percent and 23 percent in type IIa and type IIb patients, respectively. HDL-cholesterol increased 8 percent, but this change did not reach statistical significance. The same hypocholesterolemic effects were also seen among subjects who consumed the soy-added diet. A comparison of results at the ends of the soy periods versus the means of final values of both control periods showed differences in serum lipids that were of similar magnitudes, but not statistically significantly different. The hypocholesterolemic response to soy was significantly related to cholesterol level at entry to the study.

The study of Lovati et al. (Ref. 46) in adults with type II hypercholesterolemia provided soy protein as SF, from textured vegetable protein, in amounts varying between 70 and 105 g depending upon total energy consumed. Plasma total and LDL-cholesterol levels both decreased by 16 percent ($p<0.01$) during the period when soy protein diet was ingested compared with levels at the start of the experimental period. Changes in these parameters on the control diet were negligible. HDL-cholesterol concentrations were not documented but were reported to be unchanged on the two diet regimens.

Gaddi et al. (Ref. 35) examined the effects of replacing animal protein and non-soy plant protein with approximately 75 g soy protein from SF in a lecithinated textured soy protein, in adults with familial hypercholesterolemia. The control diet did not affect plasma lipid values during the initial experimental period. After ingestion of the soy protein diet, plasma total cholesterol decreased by 21 percent ($p<0.0l$) and LDL-cholesterol decreased by 25 percent ($p<0.01$) from levels measured after the first control diet period. HDL-cholesterol levels were unchanged. Plasma total and LDL-cholesterol returned to concentrations close to those at baseline following resumption of the control diet during the third experimental period.

b. *Studies in children.* Gaddi et al. (Ref. 34) studied children from 3 to 12 years of age with familial hypercholesterolemia. After a baseline dietary period during which subjects consumed a low lipid diet, soy protein in the form of SF replaced a portion of the animal protein intake. No significant changes in plasma lipids occurred over the duration of the baseline dietary period. Plasma total cholesterol at the end of the soy protein dietary period was 20 percent lower than at the end of the baseline dietary period ($p<0.001$). LDL-cholesterol was 24 percent lower ($p<0.01$) and HDL-cholesterol level was not affected.

Widhalm et al. (Ref. 63) examined the lipid-lowering effects of incorporating ISP (13.5–18 g protein) into food and beverage recipes in children with familial hypercholesterolemia. After the soy protein dietary periods, plasma total cholesterol was 16 percent lower ($p<0.005$) than baseline levels in the group that consumed the soy protein diet before the control diet and 18 percent lower ($p<0.001$) in the group that consumed soy last. LDL-cholesterol was also statistically significantly decreased ($p<0.001$) by 22 percent in the first group and 25 percent in the second group. During the control diet periods, total and LDL-cholesterol levels were reduced by 8 percent and 7 percent in the first group and by 12 percent and 13 percent in the second group, respectively. HDL-cholesterol was not statistically significantly affected by dietary treatment.

Laurin et al. (Ref. 45) and Jacques et al. (Ref. 42) both reported on a test of the lipid-lowering effects of ISP (28 g of soy protein) in children, 6 to 12 years of age, with familial hypercholesterolemia. Children consumed either a conventional low fat diet with 2-percent cow's milk or the same low fat diet with a soy-based beverage made with 2-percent butterfat substituted for the 2-percent cow's milk. Comparisons between the two treatment groups indicated that total and LDL-cholesterol levels were not altered. HDL-cholesterol level was increased 4 percent ($p<0.04$) with soy protein compared to cow's milk.

c. *Summary—Subjects with Type II or familial hypercholesterolemia.* Each of the ten studies of the effects of soy protein in subjects with severe (type II or familial) hypercholesterolemia employed diets low in saturated fat and cholesterol (Refs. 33, 35, 46, 55, 56, 60, 64, 34, 42 and 45 (1 trial), and 63), and most subjects had been consuming such a therapeutic diet prior to the study. Six of the ten trials were conducted by workers from the same group (Refs. 55, 33, 56, 46, 35, and 34). Most used SF in TVP as the source of soy protein, in amounts ranging from 14 to 105 g (Refs. 33, 56, 60, 46, 35, 34, and 63); the remainder used ISP as the source of soy protein, in amounts ranging from 28 to 60 g (Refs. 55, 64, and 42 and 45 (1 trial)). In all the studies conducted in adults (Refs. 33, 35, 46, 55, 56, 60, and 64), using both fixed sequence and crossover study designs, large and statistically significant decreases in both total and LDL-cholesterol levels were observed in response to consumption of diets containing soy protein. In the six trials in which they were measured, HDL-cholesterol levels were either not statistically significantly affected (Refs. 33, 64, 60, 46, and 35) or were statistically significantly increased (Ref. 56).

In the studies conducted in children with familial hypercholesterolemia, two of the three trials demonstrated statistically significant decreases from baseline levels in total and LDL-cholesterol during the periods when soy protein diets were consumed (Refs. 34 and 63). However, interpretation of these findings is complicated by uncertainty about the control of intake of other dietary constituents, especially saturated fat and cholesterol. In the study reported by Laurin et al. and Jacques et al. (Refs. 45 and 42), differences in these dietary components were controlled. With diets providing 12 percent of kcal from saturated fat and 163 to 180 mg of cholesterol, plasma total and LDL-cholesterol levels were not statistically significantly different, but the HDL-cholesterol level was statistically significantly higher, on the soy diet than on the cow's milk diet.

3. Epidemiologic Evidence on Soy Protein and Blood Lipids

The petitioner also submitted one epidemiologic study by Nagata et al. (Ref. 65) that described the relationship between soy product and soy protein intake and serum total cholesterol concentrations in Japanese men and women. Participants in this study were 1,242 men and 3,596 women from the Takayama Study, a prospective cohort study on the impact of diet and lifestyle on cancer, who attended the annual health checkup program between April and October 1992. Data regarding food intake were collected by a validated, semiquantitative food frequency questionnaire (FFQ). Blood samples were also taken for each subject and analyzed for total cholesterol concentrations. Soy products identified in the FFQ included tofu (plain, fried, deep-fried, or dried), miso, fermented soybeans, soy milk, and boiled soybeans. The estimated amount of soy protein consumed from these sources was 8.00 ± 4.95 g/day for men and 6.88

± 4.06 g/day for women. The authors noted that their FFQ may underestimate soy product intake; they also estimated that 4 to 9 g additional soy protein may be consumed daily from soy protein added to meats and fish pastes that was not accounted for in the FFQ. Thus, analyses were presented in terms of relative soy protein intake. Using energy-adjusted means for quartiles of soy protein intake, a statistically significant negative trend was observed for lower serum total cholesterol concentrations with higher levels of soy protein intake ($p<0.0001$ for both men and women). The analysis for men was controlled for age, smoking status, and total energy, protein, and fat intake. The analysis for women was controlled for age, menopausal status, body mass index, and intake of energy and vitamin C. Further adjustments for physical activity, coffee and tea consumption, and intakes of cholesterol, carbohydrates, fiber, and vitamin E were performed and results were not affected. Between the 1st and 4th quartiles in men, total cholesterol was lower by 12 mg/dL with a 9.6-g increase in soy protein intake. For women, total cholesterol was lower by 9 mg/dL with a 7.9-g increase in soy protein intake.

4. Meta-analysis of Studies of Soy Protein and Blood Lipids

The petitioner presented the results of a 1995 meta-analysis (Ref. 66) of the effect of soy protein on blood lipids. While the role of ''research synthesis'' studies, including meta-analyses, is of interest, it is as yet unresolved. The appropriateness of such analytical techniques to establish diet/health relationships in particular is not known. There are on-going efforts to identify criteria and critical factors to consider in both conducting and using such analyses, but this science is still emerging. Therefore, the meta-analysis did not weigh heavily within the body of evidence for this relationship.

In summary, Anderson et al. (Ref. 66) pooled data from studies that were deemed comparable in methodology in order to perform a meta-analysis of the effect of soy protein on blood lipids. Of the 37 publications identified by these investigators that presented data on soy protein and lipid changes, 29 met the criteria of using either ISP or texturized soy protein as the soy protein source, employing either a parallel or crossover design, and providing initial or baseline cholesterol values to allow calculation of decreases. These 29 publications reported the findings from 38 separate trials. Each of these publications was included in the petition and was considered for review individually by FDA as described previously. Thirty-four of the trials were conducted among adults and four among children. Study samples included individuals with normal blood cholesterol levels as well as those with mildly to severely elevated levels. Twelve of the trials were conducted in subjects with familial hypercholesterolemia.

The specific analytical approach is described in Anderson et al. (66). Based on examining the difference from baseline between the soy protein and control protein groups, the analysis indicated that soy protein consumption statistically significantly decreased total cholesterol for the pooled data by 9.3 percent and LDL-cholesterol by 12.9 percent. HDL-cholesterol was increased by a net of 2.4 percent with soy protein ingestion, but this change was not statistically significant. This analysis also suggested that the initial level of serum total cholesterol was the most important determinant of serum lipid response to soy protein. When changes in total and LDL-cholesterol were examined by quartile of baseline cholesterol concentration, a progressively greater magnitude of change was observed from the lowest to the highest quartiles. Additional analyses indicated that the type and amount of soy protein consumed and type of background diet did not substantially influence the results.

To examine further the effects of the type and amount of soy protein, an analysis was performed using changes observed with the soy diet alone instead of net changes as the outcome variable. Initial serum cholesterol concentration was also the major determinant of effects in this model, but statistically significant effects ($p=0.02$) were also obtained for amount of soy protein. This model predicted, after adjustment for initial values and other variables, serum total cholesterol decreases of 8.9 mg/dL with 25 g/day soy protein, 17.4 mg/dL with 50 g/day of soy protein, and 26.3 mg/dL with 75 g/day of soy protein.

5. Studies of the Role Soy Isoflavones

Isoflavones are a class of naturally-occurring compounds with weak estrogenic/antiestrogenic activities that are present in a wide variety of plants. The 12 major isomers of naturally-occurring isoflavones in soybeans are genistein, genestin, 6''-*O*-acetylgenistin, 6''-*O*-malonylgenestin, diadzein, diadzin, 6''-*O*-acetyldiadzin, 6''-*O*-malonyldiadzin, glycitein, glycitin, 6''-*O*-acetylglycitin, and 6''-*O*-malonyglycitin. The levels of isoflavones in soybeans are known to vary with cultivar and growing conditions. Soy isoflavones are retained to variable degrees in soy protein products and soy foods, depending on the particular processing techniques used. For example, essentially all of the isoflavones in soy protein products can be extracted by alcohol washing, and their levels can also be reduced by repeated aqueous washings and some texturization techniques. Because of the estrogenic activities of the soy isoflavones, they have been hypothesized to contribute to the hypocholesterolemic effect of soy protein.

The petitioner submitted an unpublished study by Crouse et al. (Ref. 31, documented in Ref. 1 with corrections noted in Ref. 2) that examined the effect of soy protein containing different levels of isoflavones in hypercholesterolemic men and women (summarized in Table 1 of this document). Potential subjects were provided instruction in an NCEP Step 1 diet and followed this diet for 1 month. Subjects with qualifying serum lipid levels (LDL-cholesterol >140 mg/dL) were given a casein drink containing 25 g protein to consume in place of other protein in the NCEP Step 1 diet. Subjects compliant with this regimen were then randomized into one of five treatment groups and baseline blood lipid values were obtained. The treatment groups received 25 g protein from ISP prepared from soy with different levels of isoflavones (either 1.0, 1.6, or 2.5 mg total aglycone isoflavones/g protein), or 25 g protein from alcohol-washed ISP that contained essentially no isoflavones (0.2 mg total aglycone isoflavones/g protein) or 25 g protein from casein (no isoflavones) in beverages for 9 weeks. Dietary intake was assessed at baseline and at the end of the study. Diet was reported to be stable and comparable between groups throughout the study, with 9 percent of energy derived from saturated fat. Body weight was also stable, with no differences between groups at baseline or at the end of the trial. Results indicated the ISP containing the highest level of isoflavones significantly lowered total ($p<0.05$) and LDL-cholesterol ($p<0.05$), by 4 percent and 6 percent, respectively, while HDL-cholesterol was not altered (Table 1). Furthermore, in subjects with LDL-cholesterol in the top half of the study population, serum total and LDL-cholesterol were reduced by 9 percent ($p<0.03$) and 12 percent ($p<0.03$), respectively, by the ISP with the highest isoflavone content, and by 8 percent ($p<0.03$) and 9 percent ($p<0.03$), respectively by the ISP with the second highest isoflavone content, while HDL-cholesterol concentrations were maintained.

Baum et al. (Ref. 28) also investigated the impact in soy protein containing different levels of isoflavones on cholesterol lowering and examined whether changes in blood lipids were lasting or transient. Subjects were moderately hypercholesterolemic women, who were at least 1 year since last menstrual period, and were not taking medications known to alter lipid or bone metabolism. Following a 2-week run-in period during which subjects consumed an NCEP Step I diet, subjects were randomly assigned to one of three treatment groups consisting of 40 g protein from either ISP with 1.4 mg total aglycone isoflavones/g protein, ISP with 2.3 mg total aglycone isoflavones/g protein, or casein/nonfat dry milk for the 24-week treatment period. Although the adjusted mean difference in total serum cholesterol level was not statistically significantly different in the soy groups and the control group, there was a significant reduction of 8 to 9 percent in non-HDL (LDL plus VLDL) cholesterol in both of the ISP treatment groups (p=0.04) compared to the control group. HDL-cholesterol was also significantly increased in both soy groups compared to the control. Body weight remained stable, and dietary intake was assessed and was reported to be similar among treatment groups although details were not reported.

The petitioner concluded that these two studies (Refs. 31 and 28) provided evidence that the hypocholesterolemic effect of soy protein is dependent on processing techniques that enable retention of the naturally occurring isoflavones in conjunction with the soy protein. As additional supportive evidence for this conclusion, the petitioner cited studies of the lipid-lowering effects of soy protein with naturally occurring isoflavones in nonhuman primates (Refs. 22 and 70). In these experiments, the effects of diets including ISP with naturally occurring isoflavones compared with those of diets containing either casein or alcohol-washed ISP stripped of essentially all naturally occurring isoflavones were examined in two species of monkeys. The studies demonstrate significant depressions in total and non-HDL (LDL plus VLDL) cholesterol levels in response to diets containing unextracted ISP as compared with the diets containing casein or alcohol-washed ISP. As evidence that soy isoflavones alone, in the absence of soy protein, are ineffective in lowering blood lipids, the petitioner cited the study of Nestel et al. (Ref. 71). In that study, consumption of a tablet containing 80 mg of total aglycone isoflavones (mainly genistein and diadzein) had no impact on blood lipid profiles in postmenopausal women.

Although the petitioner suggested, based on the studies of Crouse et al. (Ref. 31) and Baum et al. (Ref. 28), that isoflavone content exceeding a certain threshold was a useful marker for soy protein that would be effective in lowering blood lipid levels, FDA has tentatively concluded that the evidence is not sufficient to establish that the presence of isoflavones accounts for or is related to the effect on blood lipids. The agency notes that there are a variety of methods for processing soy that could give rise to variable amounts of naturally-occurring isoflavones in soy protein products, and this is a possible hypothesis for explaining some of the variability in the results of human intervention studies. However, with two exceptions (Refs. 31 and 28), the studies reviewed and described in this document did not include concurrent measures of the isoflavone content of the soy protein products studied. More importantly, a recent letter to the editor from Sirtori et al. (Ref. 72), which was not included in the petition, contradicts the conclusions of Crouse et al. (Ref. 31) and Baum et al. (Ref. 28). These researchers (Ref. 72) reported that the TVP fed in their studies contained essentially no isoflavones and still considerable impact on LDL-cholesterol was observed. These studies (Refs. 33, 56, 46, 35, and 34) were conducted in subjects with type II hypercholesterolemia and all showed large and significant decreases in blood total and LDL-cholesterol levels.

Given the limited number of studies and the contradictory outcomes, FDA is not persuaded that the isoflavone component of soy protein is a relevant factor to the diet-disease relationship. Rather, FDA tentatively concludes that the evidence from a wide range of studies using differently processed soy protein is supportive of a relationship between soy protein per se and reduced risk of CHD.

6. Summary

In five (Refs. 31, 28, 27, 51, and 44) of seven (Refs. 31, 28, 27, 51, 44, and 40 (2 trials)) well-controlled studies of hypercholesterolemic subjects consuming low saturated fat and low cholesterol diets, soy protein intake was associated with statistically significant decreases in total and/or LDL-cholesterol levels, either in the entire study populations or subsets of subjects with higher initial blood lipid levels. Levels of HDL-cholesterol were found either to be unchanged (Refs. 31, 27, 51, and 40 (2 trials)) or slightly but statistically significantly increased (Refs. 28 and 44) by consumption of diets containing soy protein.

Levels of soy protein as ISP found to be effective in lowering total and LDL-cholesterol levels, in the context of a diet low in saturated fat and cholesterol, ranged in these studies from 25 to 50 g (Refs. 31, 28, 27, and 51). As whole soybean milk, 31 g of soy protein lowered LDL-cholesterol only in the subset of subjects with the highest initial LDL-cholesterol levels and LDL/HDL-cholesterol levels (Ref. 44). Diets providing 50 g of soy protein as SF did not cause significant changes from baseline for any of the blood lipids, but the decrease in total cholesterol observed after ingestion of SF was significantly greater than that on the control diet of nonfat dry milk and cellulose (Ref. 51). Diets providing 27 g of soy protein as SF in a textured product had no significant effects on blood lipid levels compared to a control diet, and a higher level (62 g) significantly lowered total cholesterol only in the experimental group fed the soy protein diet first (Ref. 40).

Three intervention studies reported on effects of soy protein in hypercholesterolemic subjects consuming ''usual'' diets that were generally high in total fat, saturated fat, and cholesterol (Refs. 37, 49, and 54). In each of these three studies, soy protein was fed in experimental diets as ISP (Refs. 37, 49, and 54). With a diet containing a very high level (99 g) of soy protein from this source (Ref. 37), statistically significant differences in both total and LDL-cholesterol were reported. Results were less consistent, showing a significant decrease in total cholesterol only in subjects with the highest baseline levels, with a relatively low level of soy protein (17 g) (Ref. 49). An intermediate level of soy protein (57 g) was found to be ineffective in lowering total cholesterol in the study of Shorey et al. (Ref. 54). (This latter study had a number of anomalous results.) HDL-cholesterol was also measured in these three studies. Changes were small and not statistically significant in two studies (Refs. 37 and 49), but HDL-cholesterol was statistically significantly decreased from baseline values by 15 percent in one study (Ref. 54).

Five intervention studies examined the effects of soy protein in normocholesterolemic subjects (Refs. 30, 36, 58, 59, and 53). Effects of soy protein on total and LDL-cholesterol were less consistent in normocholesterolemic subjects than in hypercholesterolemic subjects. As ISP, 44 g of soy protein was effective in significantly lowering total cholesterol in one study (Ref. 30) and 54 g

significantly lowered LDL-cholesterol in one study (Ref. 58). With very low initial blood lipid levels seen in some of these studies, the impact of dietary changes is considerably lessened. HDL-cholesterol was measured in four of these studies, with statistically significant increases associated with soy protein intake found in two (Refs. 58 and 59) and no statistically significant changes in two (Refs. 36 and 53).

Two intervention studies (Refs. 29 and 43) examined the hypocholesterolemic effects of soy protein versus casein in the context of hypocaloric diets fed to obese persons to achieve significant weight reduction. These two studies (Refs. 29 and 43) demonstrated large decreases in both total and LDL-cholesterol levels during hypocaloric diets that provided relatively low amounts (27 and 17 g, respectively) of soy protein. HDL-cholesterol was decreased in both soy and casein groups at the end of the first study (Ref. 29); however, only the casein group's values were significantly different ($p<0.01$) from baseline. Additionally, the decrease in HDL-cholesterol in the casein group was significantly greater ($p<0.01$) than that observed in the soy protein group. In the second study (Ref. 43), HDL-cholesterol levels were not significantly affected by dietary treatment.

In all seven intervention studies conducted in adults with type II or familial hypercholesterolemia (Refs. 33, 35, 46, 55, 56, 60, and 64), large and statistically significant decreases in both total and LDL-cholesterol levels were observed in response to consumption of diets containing soy protein. In the six trials in which they were measured, HDL-cholesterol levels were either not statistically significantly affected (Refs. 33, 64, 60, 46, and 35) or statistically significantly increased (Ref. 56). Each of these studies in adults with severe (type II or familial) hypercholesterolemia employed diets low in saturated fat and cholesterol (Refs. 33, 35, 46, 55, 56, 60, and 64) and most subjects had been consuming such a therapeutic diet prior to the study. Most trials used SF in TVP as the source of soy protein, in amounts ranging from 31 to 105 g (Refs. 33, 56, 60, 46, and 35); the remainder used ISP as the source of soy protein, in amounts ranging from 28 to 60 g (Refs. 55 and 64). Two of the three trials conducted in children with familial hypercholesterolemia demonstrated significant decreases from baseline levels in total and LDL-cholesterol during the periods when soy protein diets were consumed (Refs. 34 and 63).

Evidence from one epidemiologic study (Ref. 65) supported a significant negative trend for lower serum total cholesterol concentrations with higher levels of soy protein intake ($p<0.0001$ for both men and women). Between the first and fourth quartiles in men total cholesterol was lower by12 mg/dL with a 9.6-g increase in soy protein intake. For women, total cholesterol was lower by 9 mg/dL with a 7.9-g increase in soy protein intake.

Based on these studies, FDA tentatively finds there is scientific evidence for a consistent, clinically significant effect of soy protein on blood total and LDL-cholesterol. The hypocholesterolemic effect of soy protein is seen in addition to the effects of a low saturated fat and low cholesterol diet. The degree of lowering of blood total and LDL-cholesterol is consistently and highly dependent on initial levels, within and across studies of subjects with normal, moderately elevated, and severely elevated blood lipid levels, with persons having higher blood lipid levels showing greater effects. Soy protein consistently causes only statistically nonsignificant effects or slight elevations in HDL-cholesterol levels. The intervention studies suggest that a minimum level of approximately 25 g of soy protein is needed to have a clinically significant effect on total and LDL-cholesterol levels. These conclusions, drawn from the review of the individual, well controlled studies, are also supported by the meta-analysis of Anderson et al. (66).

IV. Decision To Propose a Health Claim Relating Soy Protein to Reduction in Risk of CHD

The petition provided and FDA reviewed information on pertinent human studies that evaluated the effects on serum cholesterol and LDL-cholesterol levels from dietary intervention with soy protein in subjects with normal to elevated serum cholesterol levels.

FDA tentatively concludes that, based on the totality of publicly available scientific evidence, there is significant scientific agreement to support the relationship between consumption of soy protein included in a diet low in saturated fat and cholesterol and the risk of CHD. The strongest evidence for the effect of soy protein on the risk of CHD is provided by studies that measured the effect of dietary soy protein consumption on the two major risk factors for CHD, total and LDL-cholesterol.

In most intervention trials in subjects with total cholesterol<300 mg/dL, soy protein was found to reduce total and/or LDL-cholesterol levels to a clinically significant degree (Refs. 31, 28, 27, 51, 44, 37, 49, 30, 58, 29, and 43). Moreover, HDL-cholesterol levels were unchanged (Refs. 31, 27, 51, 40, 37, 49, 36, and 53) or slightly increased (Refs. 28, 44, 58, and 59). In some cases (Refs. 27, 44, and 49), decreases in total and LDL-cholesterol were statistically significant only in subsets of subjects with the higher initial blood lipid levels. Results in normocholesterolemic subjects (Refs. 30, 36, 58, 59, and 53) were more variable than in hypercholesterolemic subjects (31, 28, 27, 51, 44, 40, 37, 49, 54, 29, and 43). The outcome of an epidemiologic study (Ref. 65) also supported a relationship between higher levels of soy protein intake and lower blood lipid levels.

Most of the studies in subjects with total cholesterol<300 mg/dL used low saturated fat and low cholesterol diets (Refs. 31, 28, 27, 51, 44, 30, 36, 53, 29, and 43), but some used ''usual'' diets (Refs. 37, 49, 54, 36, 58, and 59). Although soy protein was found to lower blood lipid levels in some of the studies using ''usual'' diets, hypocholesterolemic effects of soy protein were more consistently observed with diets low in saturated fat and cholesterol. In some studies (especially those without run-in periods) (Refs. 40 and 54), the control low saturated fat and low cholesterol diets induced significant decreases in blood lipid levels making it difficult to detect any additional effect of soy protein. At the same time, in two studies in which soy protein containing hypocaloric diets were compared to similar diets without soy (Refs. 29 and 43), only the soy protein containing diets induced significant changes in blood lipid levels. Given the variability of amounts and forms in which soy protein was provided in the diets, the response of blood lipid levels appears robust.

Data from studies of adults with type II and familial forms of hypercholesterolemia (and total cholesterol levels in excess of 300 mg/dL) (Refs. 55, 33, 64, 56, 64, 46, and 35) were more consistent than studies in persons with lower blood lipid levels in showing large and statistically significant decreases in total and LDL-cholesterol, accompanied by no changes or slight increases in HDL-cholesterol levels. Nearly all of the subjects in these trials consumed low saturated fat and low cholesterol diets during the studies and had consumed such diets prior to studies with soy protein.

Soy protein was tested in a variety of food forms (as soy beverages, formulated into meat and dairy product analogs, added to soups, or baked into foods, such as muffins and breads) but produced fairly consistent results

regardless of the food form fed and apparent differences in processing techniques.

FDA tentatively concludes, based on the evidence submitted and reviewed, that soy protein, included in a diet low in saturated fat and cholesterol, can lower blood total and LDL-cholesterol levels, without adversely affecting HDL-cholesterol levels. The agency also tentatively concludes that the effect is due to soy protein per se and is not consistently related to the presence or absence of isoflavones. The intervention studies suggest that a minimum level of approximately 25 g of soy protein is needed to have a clinically significant effect on total and LDL-cholesterol levels.

Based on the totality of the scientific evidence presented in the petition, the agency tentatively concludes that there is significant scientific evidence to show that soy protein, included in a diet low in saturated fat and cholesterol, will help reduce serum lipids, and that such reductions may reduce the risk of CHD. In the majority of clinical studies evaluating soy products, total and LDL-cholesterol were the lipid fractions shown to be the most affected by soy protein intervention. As part of a diet low in saturated fat and cholesterol, regular consumption of soy protein, in an amount to provide 25 g/day, resulted in reduced total and LDL-cholesterol levels in subjects with normal and elevated serum cholesterol levels. As stated in section III.A of this document, Federal Government and other reviews have concluded that there is substantial epidemiologic and clinical evidence that high blood levels of total cholesterol and LDL-cholesterol represent major contributors to CHD (56 FR 60727 at 60728, and Refs. 4 through 7). Dietary factors that decrease total cholesterol and LDL-cholesterol will affect the risk of CHD (Refs. 4 through 7).

Given all of this evidence, the agency is proposing a health claim on the relationship between soy protein and reduced risk of CHD.

V. Description and Rationale for Components of Health Claim

A. Relationship Between Soy Protein and CHD and the Significance of the Relationship

Proposed § 101.82(a) describes the relationship between diets low in saturated fat and cholesterol containing soy protein and the risk of CHD. In proposed § 101.82(a)(1), the agency recounts that CHD is the most common and serious form of CVD, and that CHD refers to diseases of the heart muscle and supporting blood vessels. The proposed section also notes that high blood total and LDL-cholesterol levels are associated with increased risk of developing CHD and identifies the levels of total cholesterol and LDL-cholesterol that would put an individual at high risk of developing CHD, as well as those serum lipid levels that are associated with borderline high risk. This information will assist consumers in understanding the seriousness of CHD.

In proposed § 101.82(a)(2), the agency recounts that populations with a low incidence of CHD tend to have low blood total and LDL-cholesterol levels. It states that these populations also tend to have dietary patterns that are low in total fat, saturated fat, and cholesterol and high in plant foods that contain fiber and other components. This information is consistent with that provided in the authorized health claim for fruits, vegetables, and grain products and CHD (§ 101.77) and so the agency believes that this information provides a basis for a better understanding of the numerous factors that contribute to the risk of CHD and the relationship with soy protein and diets low in saturated fat and cholesterol.

Proposed § 101.82(a)(3) states that diets low in saturated fat and cholesteral may reduce the risk of CHD. The paragraph further states that soy protein, when added to such a diet, may also help reduce the risk of CHD.

Proposed § 101.82(b) describes the significance of the diet-disease relationship. In proposed § 101.82(b)(1), the agency recounts that CHD remains a major public health concern in the United States because the disease accounts for more deaths than any other disease or group of diseases. The claim states that early management of modifiable risk factors for CHD is a major public health goal that can assist in reducing the risk of CHD. This information is consistent with the evidence that lowering blood total and LDL-cholesterol levels reduces the risk of CHD (56 FR 60727, 58 FR 2739, and Refs. 4 through 8).

In proposed § 101.82(b)(2), the significance of the relationship between soy protein and CHD risk factors in context of the total diet is discussed. The agency recounts that many Americans' intakes of saturated fat and cholesterol exceed recommended levels, and it summarizes public health recommendations for the diet (56 FR 60727 at 60738 and § 101.75(b)(3)). This paragraph also states that scientific evidence demonstrates that diets low in saturated fat and cholesterol and that contain soy protein are associated with reduced blood lipids. FDA tentatively concludes that the latter statement is scientifically valid based on the evidence that it has reviewed on this nutrient-disease relationship.

B. Nature of the Claim

In proposed § 101.82(c)(1), FDA is proposing to require that all of the general requirements for health claims set out in § 101.14 be met. This provision is consistent with the provisions of the other specific health claim regulations in 21 CFR part 101, subpart E.

In proposed § 101.82(c)(2)(i), FDA is proposing to authorize a health claim on the relationship between diets that contain soy protein and are low in saturated fat and cholesterol and the risk of CHD. The agency is proposing to do so based on its review of the scientific evidence on this nutrient-disease relationship, which shows that diets that contain soy protein and are low in saturated fat and cholesterol help to reduce total and LDL-cholesterol levels, especially in individuals with elevated blood total cholesterol (Refs. 31, 28, 27, 51, 44, 37, 49, 30, 58, 29, 43, 55, 33, 64, 56, 64, 46, and 35). This result is significant for the risk of heart disease because elevated levels of total and LDL-cholesterol are associated with increased risk of CHD (Refs. 4 through 7).

Most of the scientific evidence for an effect of soy protein on blood lipid levels was provided by studies that used diets low in saturated fat and cholesterol. Although soy protein was found to lower blood lipid levels in some of the studies using ''usual'' diets (Refs. 37, 49, and 58), hypocholesterolemic effects of soy protein were more consistently observed with diets low in saturated fat and cholesterol.

Moreover, as stated in section V.A of this document, CHD is a major public health concern in the United States, and the totality of the scientific evidence provides strong and consistent support that diets high in saturated fat and cholesterol are associated with elevated levels of blood total and LDL-cholesterol and, thus, CHD (56 FR 60727 at 60737). Dietary estimates for American adults show that the average saturated fat intakes of American adults are about 13 percent of calories, total fat intakes are about 37 percent of calories, and average cholesterol intakes range from 300 to over 400 mg daily for adult men and women (56 FR 60727 at 60738). The current intakes of saturated fat and total fat are thus well in excess of recommended goals of less than 10 percent and 30 percent of calories.

Dietary guidelines from both Government and private scientific bodies conclude that the majority of the American population would benefit from decreased consumption of dietary saturated fat and cholesterol (Refs. 4 through 7). The results of several studies showed that daily consumption of soy protein lowered total cholesterol and LDL-cholesterol, and the effects of dietary intake of soy protein were evident when the diets were low in saturated fat and cholesterol (Refs. 31, 28, 27, 51, 44, 30, 29, and 43). Thus, the agency tentatively finds that it will be more helpful to Americans' efforts to maintain healthy dietary practices if the effect of soy protein on serum lipids is characterized in the context of a diet low in saturated fat and cholesterol.

In § 101.82(c)(2)(i)(A), the agency is proposing to require, consistent with other health claims, that the relationship be qualified with the terms ''may'' or ''might.'' These terms are used to make clear that not all persons can necessarily expect to benefit from these dietary changes (56 FR 60727 at 60740 and 58 FR 2552 at 2573). The requirement that the claim use the term ''may'' or ''might'' to relate the ability of soy protein to reduce the risk of heart disease is also intended to reflect the multifactorial nature of the disease.

In § 101.82(c)(2)(i)(B), the agency is proposing to require, consistent with other authorized health claims, that the terms ''coronary heart disease'' or ''heart disease'' be used in specifying the disease. These terms are commonly used in dietary guidance materials, and therefore they should be readily understandable to the consumer (56 FR 60727 at 60740 and 58 FR 2552 at 2573).

In § 101.82(c)(2)(i)(C), the agency is proposing that the claim specify the substance as ''soy protein.'' Based on its review of the scientific evidence submitted with the petition, the agency tentatively concludes that there is significant scientific agreement that diets low in saturated fat and cholesterol that contain soy protein may help to reduce blood total and LDL-cholesterol levels, the major modifiable risk factors for CHD (Refs. 31, 28, 27, 51, 44, 37, 49, 30, 58, 29, 43, 55, 33, 64, 56, 64, 46, and 35). As discussed in section III.C.5 of this document, FDA did not find persuasive the limited and contradictory evidence that soy isoflavones are a relevant factor in the diet-disease relationship persuasive. Therefore, FDA has tentatively concluded that evidence from a wide range of studies supports a relationship between soy protein per se and reduced risk of CHD.

As discussed previously, the agency tentatively finds that for the public to understand fully, in the context of the total daily diet, the significance of consumption of soy protein on the risk of CHD (see section 403(r)(3)(B)(iii) of the act), information about the total diet must be included as part of the claim. Therefore, in § 101.82(c)(2)(i)(D), the agency is proposing to require that the claim include the fact that the effect of dietary consumption of soy protein on the risk of CHD is evident when it is consumed as part of a healthy diet and that, consistent with other authorized health claims, the fat component of the diet be specified as ''saturated fat'' and ''cholesterol.'' Based on its review of the scientific evidence submitted with the petition, the agency tentatively concludes that there is significant scientific agreement that diets containing soy protein and low in saturated fat and cholesterol are associated with reduced blood total and LDL-cholesterol levels.

Proposed § 101.82(c)(2)(i)(E), consistent with other authorized health claims, requires that the claim not attribute any degree of risk reduction of CHD to consumption of diets low in saturated fat and cholesterol that contain soy protein. None of the studies that the agency reviewed provide a basis for determining the percent reduction in risk of CHD likely from consuming diets that contain soy protein and are low in saturated fat and cholesterol. Also consistent with other authorized claims, proposed § 101.82(c)(2)(i)(F) requires that the claim not imply that consumption of diets low in saturated fat and cholesterol and that contain soy protein is the only recognized means of reducing CHD risk.

Proposed § 101.82(c)(2)(i)(G) requires that the claim specify the daily dietary intake of soy protein needed to reduce the risk of CHD and the contribution one serving of the product makes to achieving the specified daily dietary intake. This requirement is consistent with requirements set forth in § 101.81.

In the studies showing a statistically significant effect of soy protein on total or LDL-cholesterol, the amounts fed ranged from 17 to 105 g/day (Refs. 31, 28, 27, 51, 44, 37, 49, 30, 58, 29, 43, 55, 33, 64, 56, 64, 46, and 35). In proposing 25 g/day as an effective daily intake of soy protein, the petitioner relied on the meta-analysis by Anderson et al. (Ref. 65) and noted that the estimate suggested by the meta-analysis was confirmed by the recent study of Crouse et al. (Ref. 31) that found reductions in total and LDL-cholesterol of 4 and 6 percent, respectively, with ingestion of 25 g/day of soy protein containing high levels of isoflavones.

FDA notes that, although none of the studies reviewed attempted to determine an effective or optimal amount of soy protein, the study by Sirtori et al. (Ref. 56) suggests the existence of a dose-response. In that study of subjects with type II hypercholesterolemia, total cholesterol levels were reduced by 13 and 19 percent, and LDL-cholesterol levels were reduced by 18 and 23 percent, compared to control by ingestion of 30 and 60 g/day of soy protein, respectively. With levels of soy protein intake lower than the proposed effective amount, findings have been variable. Mercer et al. (Ref. 49) found a statistically significant reduction in total cholesterol in response to 17 g/day of soy protein only in those subjects with high initial values. Feeding the same amount (17 g/day) of soy protein in a hypocaloric diet, however, Jenkins et al. (Ref. 43) found statistically significant reductions of 10 and 17 percent in total and LDL-cholesterol, respectively. With 25 g/day of soy protein, Bakhit et al. (Ref. 27) found a statistically significant reduction in total cholesterol (about 8 percent) in subjects with blood cholesterol levels greater than 220 mg/dL. Crouse et al. (Ref. 31) found that 25 g of soy protein that contained a high level of isoflavones significantly lowered total ($p<0.05$) and LDL-cholesterol ($p<0.05$), by 4 percent and 6 percent, respectively. Furthermore, in subjects with LDL-cholesterol in the top half of the study population, serum total and LDL-cholesterol were reduced by 9 percent ($p<0.03$) and 12 percent ($p<0.03$), respectively, by soy protein with the highest isoflavone content, and by 8 percent ($p<0.03$) and 9 percent ($p<0.03$), respectively, by soy protein with the second highest isoflavone content. Although Holmes et al. (Ref. 40) did not find statistically significant changes in blood lipids with 27 g of soy protein, using 28 g of soy protein in a hypocaloric diet, Bosello et al. (Ref. 29) observed decreases of 16 percent from baseline in both total and LDL-cholesterol ($p<0.01$). With 31 g of soy protein, Kurowska et al. (Ref. 44) found an 11-percent reduction in LDL-cholesterol in subjects with the highest initial LDL-cholesterol levels and LDL/HDL-cholesterol ratios. As a substitution or as an addition, Verillo et al. (Ref. 60) found 31 g of soy protein produced large (>20 percent) reductions in both total and LDL-cholesterol in subjects with type II hypercholesterolemia.

Based on these data that support a dose-response and that show clinically significant reductions in total and LDL-

cholesterol with soy protein ingestion in the range of 17 to 31 g/day, and recognizing that the hypocholesterolemic effects of soy protein are highly dependent on initial blood lipid levels, the agency has tentatively accepted that 25 g/day represents a reasonable effective amount of soy protein. In addition, an amount of 25 g/day of soy protein represents half of the Reference Daily Intake (RDI) of 50 g for protein and is a reasonable level of consumption in the context of the total daily diet. Thus, FDA tentatively concludes that the amount of soy protein associated with reduction in total and LDL-cholesterol levels and, thus, with reduced risk of CHD is 25 g or more of soy protein per day. The agency is asking for comments on this tentative determination.

C. Nature of the Substance

Proposed § 101.82(c)(2)(ii)(A) indicates that soy protein from the legume seed *Glycine max* is the substance that is the subject of this claim.

Proposed § 101.82(c)(2)(ii) (B) sets out FDA's tentative decision that soy protein when evaluated for compliance purposes by the agency will be measured using the Association of Official Analytical Chemists International (AOAC) official method of analysis No. 988.10.

The petitioner proposed that measurement of total soy isoflavones be used as a marker for the content of soy protein in foods and as an indicator of the effectiveness of soy protein products in reducing blood cholesterol. As discussed in section C.III.5 of this document, FDA disagrees with the petitioner's conclusions regarding the significance of soy isoflavones with respect to the observed hypocholesterolemic effects of soy protein. Accordingly, FDA finds the proposed methodology to assess isoflavones irrelevant. The AOAC method that FDA is proposing instead is an enzyme-linked immunosorbant assay that detects soy protein in raw and heat-processed meat products. With this assay, samples are compared to standard commercial soy protein and appropriate blanks. The method is described as semi-quantitative, but it can be quantitative when the nature of the soy protein in the samples is known and the assay is calibrated accordingly. The sample extraction procedure, which involves preparation of an acetone powder, has been shown to be appropriate for a complex food matrix (meat). FDA believes, therefore, that this assay should also be suitable for other food matrices. FDA is requesting comments on the suitability of this method for assuring that foods bearing the health claim contain qualifying levels of soy protein.

D. Nature of the Food

Proposed § 101.82(c)(2)(iii)(A) requires that the food bearing the health claim contain at least 6.25 g of soy protein per reference amount customarily consumed (RACC) of the food product.

Using 25 g of soy protein as the qualifying amount for a CHD claim, the petitioner suggested that a single serving of a soy protein-containing product (i.e., 1 RACC) should provide 1/4 of this amount (based on 4 servings a day). Thus, a soy protein-containing product would have to contain at least 6.25 g soy protein (1/4 x 25 g) per RACC. The petitioner stated that this approach is reasonable because it would permit a wide variety of low fat, soy protein containing products to bear the health claim. The petitioner provided a list of products on the market that currently meet the proposed requirements and a list of products that could be modified to meet them (Ref. 1, Appendix V).

The agency has generally made the assumption that a daily food consumption pattern includes three meals and a snack (see 58 FR 2302 at 2379, January 6, 1993). Because of the wide variety of types of foods that could contain qualifying levels of soy protein (baked goods, tofu, soy beverages and shakes, meat analogs), the agency has tentatively concluded that the assumption of 4 servings/d of soy protein containing foods is reasonable. Therefore, the agency tentatively finds that use of the qualifying criterion set forth in the petition for this proposed rule is appropriate and is proposing this level in this document. The qualifying level of protein, 6.25 g/RACC, exceeds the amount required for a food to qualify as a ''good source'' of protein, i.e., 10 percent of the RDI of 50 g or 5 g/RACC).

In § 101.82(c)(2)(iii)(B), the agency is proposing, consistent with other authorized heart disease health claims, that foods bearing the health claim meet requirements for ''low saturated fat,'' ''low cholesterol,'' and ''low fat.'' In the preamble to the final rule on fruits, vegetables, and grain products and heart disease (§ 101.77, 58 FR 2552 at 2572), the agency stated that populations with diets rich in these low saturated fat and low cholesterol foods experience many health advantages, including lower rates of heart disease. In the preamble to the proposed rule on dietary lipids and heart disease (56 FR 60727 at 60739), the agency stated that while total fat is not directly linked to increased risk of CHD, it may have significant indirect effects. Foods that are low in total fat facilitate reductions in intakes of saturated fat and cholesterol to recommended levels. Therefore, the agency tentatively concludes that proposed § 101.82(c)(2)(iii)(B) sets forth an appropriate requirement for food to be eligible to bear the soy protein and CHD claim.

E. Optional Information

FDA is proposing in § 101.82(d)(1) that the claim may state that the development of heart disease depends on many factors and, consistent with authorized CHD health claims, may list the risk factors for heart disease that are listed in §§ 101.75(d)(1), 101.77(d)(1), and 101.81(d)(1). The agency is also proposing, in response to the petition, that the claim may provide additional information about the benefits of exercise and body weight management. This additional information can provide a context that is useful for an understanding of the relationship between soy protein and heart disease, but manufacturers should be cautioned that it should not be presented in a way that is misleading to the consumer.

In proposed § 101.82(d)(2), consistent with §§ 101.75(d)(2), 101.77(d)(2), and 101.81(d)(2), FDA is providing that the claim may state that the relationship between a diet high in soy protein and reduced risk of heart disease is through the intermediate link of ''blood cholesterol'' or ''blood total cholesterol'' and ''LDL- cholesterol.'' The relationship between soy protein and reduced blood total cholesterol and LDL-cholesterol is supported by the scientific evidence presented in this proposal.

In § 101.82(d)(3), the agency is proposing that, consistent with §§ 101.75(d)(3), 101.77(d)(3), and 101.81(d)(3), the claim may include information from § 101.82(a) and (b). These paragraphs summarize information regarding the relationship between diets high in soy protein and the risk of CHD and about the significance of that relationship. This information helps to convey the seriousness of CHD and the role that a diet high in soy protein can play to help reduce the risk of CHD.

The agency is proposing that the claim may include any of the optional information authorized to be included in §§ 101.75(d)(5), (d)(6), and (d)(7), 101.77(d)(5), (d)(6), and (d)(7), and 101.81(d)(5), (d)(6), and (d)(7). The health claim may state that diets high in soy protein and low in saturated fat and cholesterol are part of a dietary pattern

that is consistent with dietary guidelines for Americans. The claim may state that individuals with elevated serum lipids should consult their physicians for medical advice and treatment and may include information on the prevalence of CHD in the United States. The intent of this information is to provide consumers with information that will help them understand the seriousness of CHD in the United States and to help them understand that diets high in soy protein are consistent with dietary guidelines.

F. Model Health Claims

In proposed § 101.82(e), FDA is providing model health claims to illustrate the requirements of new § 101.82. FDA emphasizes that these model health claims are illustrative only. These model claims illustrate the required, and some of the optional, elements of the proposed rule. If the agency authorizes a claim about the relationship between soy protein and CHD, manufacturers will be free to design their own claim so long as it is consistent with § 101.82(c).

In §§ 101.82(e)(1) and (e)(2), the model claim illustrates all of the required elements of the proposed health claim. The claim states ''25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies ———— grams of soy protein.'' or ''Diets low in saturated fat and cholesterol that include 25 grams of soy protein may reduce the risk of heart disease. One serving of [name of food] provides ———— grams of soy protein.''

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(k) 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.

VII. Analysis of Impacts

A. Cost–Benefit Analysis

FDA has examined the impacts of the proposed rule under Executive Order 12866. Executive Order 12866 directs Federal agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). According to Executive Order 12866, a regulatory action is ''economically significant'' if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs. A regulation is considered ''significant'' under Executive Order 12866 if it raises novel legal or policy issues. FDA finds that this proposed rule is neither an economically significant nor a significant regulatory action as defined by Executive Order 12866.

In addition, in accordance with the Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801(a)(1)(A)(ii)), the Administrator of the Office of Information and Regulatory Affairs of the Office and Management and Budget (the Administrator) has determined that this proposed rule is not a major rule for the purpose of congressional review. A major rule for this purpose is defined in 5 U.S.C. 804(2) as one that the Administrator has determined has resulted or is likely to result in: (1) An annual effect on the economy of $100,000,000 or more; or (2) a major increase in costs for prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or (3) significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or export markets.

This proposed rule will give firms the option of making certain label claims involving soy protein. No costs will be generated by this proposed rule because it will not require any labels to be changed or any product to be reformulated. Firms will only relabel or reformulate products if the benefits to those firms outweigh the costs. Social benefits may be generated by this proposed rule because the value some consumers place on the information provided in these claims may be greater than the cost to industry of making these claims. In general, consumers may value this type of information because it will enable them to eat a healthier diet. Consumers may value this type of information presented on product labels, in particular, because it would obviate the need to consult other sources of information and because it may reassure consumers who are aware of the role of FDA in regulating health claims on product labels that the information is truthful, not misleading, and scientifically valid.

Consumer valuation of this information will reflect the value that consumers place on reducing the likelihood of CHD and the perceived usefulness of this information for reducing the likelihood of CHD. However, consumers may either underestimate or overestimate the usefulness of this information in reducing the likelihood of CHD. Therefore, another metric for valuing the social benefits of this proposed rule is the health care costs avoided by the reduction in CHD-related disease and disability made possible by this proposed rule. If consumers were aware of these health care costs and had an accurate notion of the likelihood that such costs could be avoided by using the information provided in the claims allowed by this proposed rule, then consumer valuation of this information would be at least as great as the value of any health care costs avoided. The value of the information might be greater because some consumers might value the information but might not choose to modify their behavior so as to reduce the likelihood of CHD.

In general terms, the relevant regulatory options available to FDA are as follows: (1) Allow this claim to be made under a broader set of conditions than those specified in this proposed rule (e.g., with fewer required elements in the claim, or with a lower level of soy protein in a serving of food), and (2) allow this claim to be made under a more restricted set of conditions than those specified in this rule (e.g., more required elements or higher levels of soy protein). Neither of these alternatives would generate net costs because, like the proposed action, firms would only relabel or reformulate products if the benefits to those firms outweigh the costs. These options would generate higher benefits than the proposed action if allowing this claim to be made under either a broader set of conditions or more restricted set of conditions than the proposed conditions would provide consumers with more valuable information (that would nonetheless be truthful, not misleading, and scientifically valid) or would make possible a greater reduction in health care costs than would the proposed action. FDA tentatively believes that no alternative conditions exist that would render the net benefits of this proposed rule greater than the proposed conditions. In particular, FDA believes that the information proposed to be required in a health claim about the relationship between soy protein and CHD is the minimum necessary for the claim to be truthful, not misleading, and

scientifically valid, thereby maximizing the likelihood that qualifying foods will be labeled with the claim and that consumers will be able to use the information. Similarly, FDA believes that the amount of soy protein proposed to be required for a food bearing this claim will allow both the claim to appear on a significant number of foods and consumers who use the claim, in the aggregate, to benefit from the use of soy protein in their diet. However, FDA requests comments and supporting information on any modifications of the conditions under which this claim is allowed that would increase the net benefits of this proposed rule.

B. Small Entity Analysis

FDA has examined the impacts of this proposed rule under the Regulatory Flexibility Act (5 U.S.C. 601–612). The Regulatory Flexibility Act requires Federal agencies to consider alternatives that would minimize the economic impact of their regulations on small businesses and other small entities. No costs will be generated by this proposed rule because it will not require any labels to be changed, or any product to be reformulated. Therefore, small businesses will only relabel or reformulate products if the benefits (e.g., increased sales of their products) to those small businesses outweigh the costs. Accordingly, under the Regulatory Flexibility Act) (5 U.S.C. 605(b)), the Commissioner of Food and Drugs certifies that this proposed rule, if issued, will not have a significant economic impact on a substantial number of small entities.

VIII. Paperwork Reduction Act

FDA tentatively concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Rather, the proposed food labeling health claim on the association between soy protein and coronary heart disease would be a ''public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

IX. Effective Date

FDA is proposing to make these regulations effective upon publication in the **Federal Register** of a final rule based upon this proposal.

X. Comments

Interested persons may, on or before January 25, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XI. References

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

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List of Subjects in 21 CFR Part 101

Food labeling, Incorporation by reference, Nutrition, Reporting and recordkeeping requirements.

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

PART 101—FOOD LABELING

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

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371.

2. New § 101.82 is added to subpart E to read as follows:

§ 101.82 Health claims: Soy protein and risk of coronary heart disease (CHD).

(a) *Relationship between diets that are low in saturated fat and cholesterol and that include soy protein and the risk of CHD.* (1) Cardiovascular disease means diseases of the heart and circulatory system. CHD is one of the most common and serious forms of cardiovascular disease and refers to diseases of the heart muscle and supporting blood vessels. High blood total cholesterol and low density lipoprotein (LDL)-cholesterol levels are associated with increased risk of developing CHD. High CHD rates occur among people with high total cholesterol levels of 240 milligrams per deciliter (mg/dL) (6.21 (millimole per liter (mmol/L))) or above and LDL-cholesterol levels of 160 mg/dL (4.13 mmol/L) or above. Borderline high risk total 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. 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 CHD.

(2) Populations with a low incidence of CHD tend to have relatively low blood total cholesterol and LDL-cholesterol levels. These populations also tend to have dietary patterns that are not only low in total fat, especially saturated fat and cholesterol, but are also relatively high in plant foods that contain dietary fiber and other components.

(3) Scientific evidence demonstrates that diets low in saturated fat and cholesterol may reduce the risk of CHD. Other evidence demonstrates that the addition of soy protein to a diet that is low in saturated fat and cholesterol may also help to reduce the risk of CHD.

(b) *Significance of the relationship between diets that are low in saturated fat and cholesterol and that include soy protein and the risk of CHD.* (1) CHD is a major public health concern in the United States. It accounts for more deaths than any other disease or group of diseases. Early management of risk factors for CHD is a major public health goal that can assist in reducing risk of CHD. High blood total and LDL-cholesterol are major modifiable risk factors in the development of CHD.

(2) Intakes of saturated fat exceed recommended levels in the diets of many people in the United States. One of the major public health recommendations relative to CHD 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. Scientific evidence demonstrates that diets low in saturated fat and cholesterol are associated with lower blood total and LDL-cholesterol levels. Soy protein, when included in a low saturated fat and cholesterol diet, also helps to lower blood total and LDL-cholesterol levels.

(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 that are low in saturated fat and cholesterol and that include soy protein with reduced risk of heart disease may be made on the label or labeling of a food described in paragraph (c)(2)(iii) of this section, provided that:

(A) The claim states that diets that are low in saturated fat and cholesterol and that include soy protein ''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) In specifying the substance, the claim uses the term ''soy protein'';

(D) In specifying the fat component, the claim uses the terms ''saturated fat'' and ''cholesterol'';

(E) The claim does not attribute any degree of risk reduction for CHD to diets that are low in saturated fat and cholesterol and that include soy protein;

(F) The claim does not imply that consumption of diets that are low in saturated fat and cholesterol and that include soy protein is the only recognized means of achieving a reduced risk of CHD; and

(G) The claim specifies the daily dietary intake of soy protein that is necessary to reduce the risk of coronary heart disease and the contribution one serving of the product makes to the specified daily dietary intake level. The daily dietary intake level of soy protein that has been associated with reduced risk of coronary heart disease is 25 grams (g) or more per day of soy protein.

(ii) *Nature of the substance.* (A) Soy protein from the legume seed *Glycine max*.

(B) FDA will measure soy protein by method No. 988.10 from the ''Official Methods of Analysis of the Association of Official Analytical Chemists International,'' 16th Ed. (1995), which is incorporated by reference in accordance with 5 U.S.C. 522(a) and 1 CFR part 51. Copies may be obtained from the Association of Official Analytical Chemists International, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877–2504, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC;

(iii) *Nature of the Food Eligible to Bear the Claim.* (A) The food product shall contain at least 6.25 g of soy protein reference amount customarily consumed of the food product;

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

(d) *Optional information.* (1) The claim may state that the development of heart disease depends on many factors and may identify one or more of the following risk factors for heart disease about which there is general scientific agreement: A family history of CHD; elevated blood total and LDL-cholesterol; excess body weight; high blood pressure; cigarette smoking; diabetes; and physical inactivity. The claim may also provide additional information about the benefits of exercise and management of body weight to help lower the risk of heart disease;

(2) The claim may state that the relationship between intake of diets that are low in saturated fat and cholesterol and that include soy protein and reduced risk of 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 that are low in saturated fat and cholesterol and that include soy protein and CHD and the significance of the relationship;

(4) The claim may state that a diet low in saturated fat and cholesterol that includes soy protein 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);

(5) 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;

(6) 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 claim.* The following model health claims may be used in food labeling to describe the relationship between diets that are low in saturated fat and cholesterol and that include soy protein and reduced risk of heart disease:

(1) 25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies ———————— grams of soy protein.

(2) Diets low in saturated fat and cholesterol that include 25 grams of soy protein may reduce the risk of heart disease. One serving of [name of food] provides ———————— grams of soy protein.

Dated: November 2, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98–30008 Filed 11–9–98; 8:45 am]

BILLING CODE 4160–01–F

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Crouse et al. (1998, submitted for pub) (Ref. 31)	CON: 9 wk NCEP Step I, low-fat (32% of E) diet with casein beverage	CON: 33 adults, 20-70 yr, with LDL-C >140 and <200 mg/dL after BASE	CON: 25 g casein	CON Prot: 15% of E Sat fat: 9% of E Chol: NR	CON v. BASE Tot-C: 0% (NS) LDL-C: 0% (NS) HDL-C: -2%(NS)
	SOY-1: 9 wk NCEP Step I, low-fat (32% of E) diet with soy beverage containing variable amounts of naturally occurring isoflavones	SOY-1: 31 as above	SOY-1: 25 g as ISP with 4.9 mg isoflavones (0.2 mg/g protein) (alcohol washed)	SOY-1 Prot: 15% of E Sat fat: 9% of E Chol: NR	SOY-1 v. BASE Tot-C: -1% (NS) LDL-C: -2% (NS) HDL-C: -2% (NS)
	SOY-2: 9 wk NCEP Step I, low-fat (32% of E) diet with soy beverage containing variable amounts of naturally occurring isoflavones	SOY-2: 31 as above	SOY-2: 25 g as ISP with 23.6 mg isoflavones (1.0 mg/d protein)	SOY-2 Prot: 15% of E Sat fat: 9% of E Chol: NR	SOY-2 v. BASE Tot-C: -3% (NS) LDL-C: -3% (NS) HDL-C: 0% (NS)
	SOY-3: 9 wk NCEP Step I, low-fat (32% of E) diet with soy beverage containing variable amounts of naturally occurring isoflavones	SOY-3: 31 as above	SOY-3: 25 g as ISP with 38.9 mg isoflavones (1.6 mg/g protein)	SOY-3 Prot: 15% of E Sat fat: 9% of E Chol: NR	SOY-3 v. BASE Tot-C: -2% (NS) LDL-C: -3% (NS) HDL-C: +2% (NS)
	SOY-4: 9 wk NCEP Step I, low-fat (32% of E) diet with soy beverage containing variable amounts of naturally occurring isoflavones	SOY-4: 30 as above	SOY-4: 25 g as ISP with 61.8 mg isoflavones (2.5 mg/g protein)	SOY-4 Prot: 15% of E Sat fat: 9% of E Chol: NR	SOY-4 v. BASE Tot-C: -4% LDL-C: -6% HDL-C: 0% (NS)
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	Parallel design, double-blinded; stratified randomization by gender and age; all subjects received 1 mon of instruction in NCEP Step 1 diet, then 1 mon run-in with casein beverage and NCEP Step 1 diet (BASE) prior to randomization to treatment groups	BASE Tot-C = 241 mg/dL		Dietary intake reported to be stable and comparable among groups throughout study	---- Analyses based on final values adjusted for differing baseline values in each dietary group; significance given v. CON

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Baum et al. (1998) (Ref. 28)	CON: 24 wk NCEP Step I, low-fat (<30% of E) with casein/nonfat dry milk incorporated into baked products, soup, and beverages	CON: 22 postmenopausal women, 49-83 yr, with Tot-C 240-300 mg/dL	CON: 40 g casein	CON Prot: NR* Sat fat: NR* Chol: <300 mg*	SOY-1 v. CON* Tot-C: NS LDL-C**: -11 mg/dL HDL-C: +5 mg/dL
	SOY-1: 24 wk NCEP Step I, low-fat (<30% of E) with soy protein (moderate isoflavone level) incorporated into baked products, soup, and beverages	SOY-1: 23 as above	SOY-1: 40 g as ISP with 56 mg isoflavones (1.4 mg/g protein)	SOY-1 Prot: NR* Sat fat: NR* Chol: <300 mg*	SOY-2 v. CON* Tot-C: NS LDL-C**: -10 mg/dL HDL-C: +4 mg/dL
	SOY-2 : 24 wk NCEP Step I, low-fat (<30% of E) with soy protein (high isoflavone level) incorporated into baked products, soup, and beverages	SOY-2: 21 as above	SOY-2: 40 g as ISP with 90 mg isoflavones (2.3 mg/g protein)	SOY-2 Prot: NR* Sat fat: NR* Chol: <300 mg*	
	---- Parallel design; randomized, double-blinded; 14 d run-in on BASE diet	----- BASE Tot-C = ~250 mg/dL No medications known to affect lipid or bone metabolism	-----	----- * Dietary intake was assessed; reported not to differ among treatment groups	----- * For adjusted mean difference ** Reported as non-HDL-C Body weight remained stable

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Bakhit et al. (1994) (Ref. 27)	CON-1: 4 wk self-selected, low-fat (26.6% of E); 4 added muffins to provide test protein and fiber	CON-1: 21 men, 23-70 yr, with Tot-C >220 mg/dL	CON-1: 25 g casein + 20 g cellulose	CON-1 Prot: 19.0% of E Sat fat: 22.0 g Chol: 314 mg	CON's or SOY's v. BASE Tot-C: NS LDL-C: NS HDL-C: NS
	SOY-1: 4 wk self-selected, low-fat (26.7% of E); 4 added muffins to provide test protein and fiber	SOY-1: same as above	SOY-1: 25 g as ISP + 20 g cellulose	SOY-1 Prot: 19.8% of E Sat fat: 21.5 g Chol: 286 mg	SOY's v. CON's Tot-C: NS LDL-C: NS HDL-C: NS
	CON-2: 4 wk self-selected, low-fat (24.6% of E); 4 added muffins to provide test protein and fiber	CON-2: same as above	CON-2: 25 g casein + 20 g soy cotyledon fiber	CON-2 Prot: 19.2% of E Sat fat: 17.4 g Chol: 260 mg	*For 11 subjects w/ Tot-C>220 mg/dL after BASE diet:* SOY-1 and SOY-2 v. BASE Tot-C: -16 and -19 mg/dL LDL-C: NS HDL-C: NS
	SOY-2: 4 wk self-selected, low-fat (26.7% of E); 4 added muffins to provide test protein and fiber	SOY-2: same as above	SOY-2: 25 g as ISP + 20 g soy cotyledon fiber	SOY-2 Prot: 19.7% of E Sat fat: 19.7 g Chol: 264 mg	SOY's v. CON's Tot-C: NS LDL-C: NS HDL-C: NS
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	Crossover; Latin square design; 2 wk run-in with BASE low-fat diet; free-living	BASE Tot-C = 222 mg/dL Note: 32% attrition			No changes in body weight or activity levels

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dl - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Potter et al. 1993 (Ref. 51)	CON: 4 wk low-fat (22.3% of E) diet; mixed protein sources with 50% from nonfat dry milk in baked products; ~20 g cellulose added	CON: 25 men, 48-78 yr, with Tot-C >200 mg/dL	CON: nonfat dry milk + cellulose	CON Prot: 18.6% of E Sat fat: NR* Chol: 220 mg	SOY-1 vs. CON Tot-C: -19 mg/dL LDL-C: -13 mg/dL (NS) HDL-C: +2 mg/dL (NS)
	SOY-1: 4 wk low-fat (24.4% of E) diet; mixed protein sources with 50% from soy protein (as SF) in baked products; ~20 g soy cotyledon fiber from SF	SOY-1: same as above	SOY-1: 50 g as SF	SOY-1 Prot: 19.3% of E Sat fat: NR* Chol: 203 mg	SOY-2 vs. CON Tot-C: -26 mg/dL LDL-C: -18 mg/dL HDL-C: 0 mg/dL (NS)
	SOY-2: 4 wk low-fat (20.8% of E) diet; mixed protein sources with 50% from soy protein (as ISP) in baked products; ~ 20 g cellulose added	SOY-2: same as above	SOY-2: 50 g as ISP + cellulose	SOY-2 Prot: 21.3% of E Sat fat: NR* Chol: 171 mg	SOY-3 vs. CON Tot-C: -25 mg/dL LDL-C: -19 mg/dL HDL-C: 0 mg/dL (NS)
	SOY-3: 4 wk low-fat (22.5% of E) diet; mixed protein sources with 50% from soy protein (as ISP) in baked products; ~20 g soy cotyledon fiber added	SOY-3: same as above	SOY-3: 50 g as ISP + soy cotyledon fiber	SOY-3 Prot: 21.4% of E Sat fat: NR* Chol: 195 mg	SOY-1 vs. BASE Tot-C: -5% (NS) LDL-C: -5% (NS) HDL-C: -1% (NS) SOY-2 vs. BASE Tot-C: -8% LDL-C: -8% (NS) HDL-C: -5% (NS) SOY-3 vs. BASE Tot-C: -8% LDL-C: -8% HDL-C: -5% (NS)
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	Crossover; Latin square design; 2 wk run-in with BASE low-fat diet; metabolic ward	BASE Tot-C = 224 mg/dL		* <10% of E Dietary fiber: CON=SOY-2>SOY-1>SOY-3	No changes in body weight or activity levels

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Kurowska et al. (1997) (Ref. 44)	CON-1: 4 wk usual, moderate-fat (29% of E) diet plus cow milk and low-fat milk dessert	CON-1: 34 adults, mean age 55 yr, with moderately elevated Tot-C (17 male)	CON-1: mixed sources + milk	CON-1 Prot: 19% of E Sat fat: 24.7 g Chol: 259 mg	CON-1, CON-2, SOY v. BASE Tot-C: NS LDL-C: NS HDL-C: +7% (for SOY)
	CON-2: 4 wk usual, moderate-fat (28% of E) diet plus skim milk, skim milk dessert, and soy oil	CON-2: same as above	CON-2: mixed sources + milk	CON-2 Prot: 19% of E Sat fat: 18.9 g Chol: 185 mg	*For 24 subjects with highest LDL-C:* SOY v. BASE Tot-C: NS LDL-C: -11% HDL-C: +9%
	SOY: 4 wk usual, moderate-fat (29% of E) diet plus soybean milk and soybean dessert	SOY: same as above	SOY: mixed sources + 31 g as whole soybean milk	SOY Prot: 19% of E Sat fat: 17.8 g Chol: 196 mg	
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	Crossover; random assignment; 4 wk run-in and 2 wk washouts with usual diet	BASE Tot-C = 265 mg/dL			

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Goldberg et al. (1982) (Ref. 37)	CON: 6 wk conventional food, high-fat (44% of E) diet; 75% of total protein from animal sources and 25% from vegetable sources other than soy	CON: 12 adults, 23-64 yr, with primary hypercholesterol-emia (7 male);	CON: mixed sources	CON Prot: 20.4% of E Sat fat: 29.3 g Chol: 215 mg	CON v. BASE Tot-C: -32 mg/dL LDL-C: -23 mg/dL HDL-C: 0 mg/dL (NS)
	SOY: 6 wk conventional food, high-fat (44% of E) diet; 75% of total protein from soy (isocaloric substitution) in meat analogs and soy milk	SOY: same as above	SOY: 99 g (est) as ISP and other sources	SOY Prot: 19.8% of E Sat fat: 27.3 g Chol: 219 mg	SOY v. BASE Tot-C: -40 mg/dL LDL-C: -33 mg/dL HDL-C: -1 mg/dL (NS) SOY v. CON Tot-C: -8 mg/dL LDL-C: -10 mg/dL HDL-C: -1 mg/dL (NS)
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	Crossover; random assignment to CON or SOY initially; 6 wk run-in with moderate-fat (37.5% of E) BASE diet; no washout	Initial Tot-C range: 227-299 mg/dL BASE Tot-C=260 mg/dL			
Mercer et al. (1987) (Ref. 49)	CON: 6 wk "usual" moderate-fat (34% of E) diet; mixed protein sources including milk	CON: 33 adults, 25-69 yr, with normal to moderately elevated cholesterol	CON: milk and other protein sources	CON Prot: 17.6% of E P/S: 0.22 Chol: 276 mg	SOY v. CON Tot-C: -2 mg/dL (NS) LDL-C: -2 mg/dL (NS) HDL-C: +1 mg/dL (NS)
	SOY: 6 wk "usual" moderate-fat (35% of E) diet; mixed protein sources with soy beverage substituted for milk	SOY: same as above	SOY: 17 g (est) as ISP and other protein sources	SOY Prot: 16.9% of E P/S: 0.29 Chol: 290 mg	For 5 subjects w/ high Tot-C: SOY v. CON Tot-C: -16 mg/dL LDL-C: -3 mg/dL (NS)
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	Crossover; random assignment to SOY or CON initially; no run-in or washout	BASE Tot-C = 221 mg/dL range 173-325 mg/dL			No significant weight changes

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Holmes et al. (1980) (Ref. 40)	CON: 3 wk moderate fat (34% of E) conventional diet; total protein comprising 40% beef, 27% other animal, and 33% vegetable sources	CON: 12 adults, 27-60 yr, with type II or type IV hyper-cholesterolemia (9 male)	CON: beef and other sources	CON Prot: 15% of E Sat fat: 8% of E Chol: 254 mg	CON v. BASE Tot-C: -36 mg/dL or -13% LDL-C: -25 mg/dL or -13% HDL-C: (NS)
	SOY: 4 wk moderate fat (34% of E) with soy substituted for beef; total protein comprising 38% soy, 31% other animal, and 31% other vegetable sources ----- Fixed sequence: CON—SOY	SOY: same as above ----- BASE Tot-C = 277 mg/dL	SOY: 27 g (est) as SF from TVP and other sources -----	SOY Prot: 15% of E Sat fat: 9% of E Chol: 254 mg -----	SOY v. CON Tot-C: -6 mg/dL (NS) LDL-C: -1 mg/dL (NS) HDL-C: -6 mg/dL (NS) -----
	CON: 3 wk moderate fat (34% of E) conventional diet; total protein comprising 71% beef and 29% vegetable sources	CON: 10 adults, 28-60 yr, with type II or type IV hyper-cholesterolemia (6 male)	CON: beef and other sources	CON Prot: 14% of E Sat fat: 9% of E Chol: 144 mg	CON (I & II) v. BASE Tot-C: - 18% (I) & NS (II) LDL-C: NS (I) & NS (II) HDL-C: NS (I) & NS (II)
	SOY: 3 wk moderate fat (35% of E) with soy substituted for beef; total protein 71% soy and 29% other vegetable sources ----- Crossover; random assignment to (I) CON—SOY or (II) SOY—CON; no run-in or washout periods	SOY: same as above ----- BASE(I)Tot-C=275 mg/dL BASE(II) Tot-C=290 mg/dL	SOY: 62 g (est) as SF from TVP and other sources -----	SOY Prot: 14% of E Sat fat: 9% of E Chol: 144 mg -----	SOY (I & II) v. BASE Tot-C: NS (I) & -19% (II) LDL-C: NS (I) & NS (II) HDL-C: NS (I) & NS (II) -----

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Shorey et al. (1981) (Ref. 54)	CON: 6 wk usual diet; prepared meals with mixed protein sources; 30-35% of E from fat	CON: 11 men, mean age 26 yr, with Tot-C >218 mg/dL	CON: mixed sources	CON Prot: 90 g Sat fat: 30 g Chol: 181 mg	CON v. BASE Tot-C: -22 mg/dL LDL-C: NR HDL-C: -4 mg/dL (NS)
	SOY: 6 wk usual diet; prepared meals with all animal protein sources replaced by soy protein; 30-35% of E from fat	SOY: 13 as above	SOY: 57 g as ISP	SOY Prot: 87 mg Sat fat: 33 g Chol: 183 mg	SOY v. BASE Tot-C: -16 mg/dL LDL-C: NR HDL-C: -8 mg/dl SOY v. CON Tot-C: +6 mg/dL LDL-C: NR HDL-C: -4 mg/dL
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	Parallel design; no run-in period	BASE Tot-C = 243 mg/dL			Note: subjects in both groups had significant weight loss; responders in both had higher protein, fat, saturated fat, and cholesterol in previous diets than in experimental diets

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Carroll et al. (1978) (Ref. 30)	CON: ~5 wk ordinary food, moderate-fat (34% of E) diet; mixed protein sources (40% animal)	CON: 10 young women, 19-25 yr, with normal Tot-C	CON: mixed sources	CON Prot: 15% of E P/S: 0.43 Chol: 168 mg	SOY v. CON Tot-C: -10 mg/dL LDL-C: NR HDL-C: NR
	SOY: ~5 wk ordinary food, moderate-fat (34% of E) diet; mixed protein sources with meats replaced by soy analogs and cow milk replaced by soy milk	SOY: same as above	SOY: 44 g (est) as ISP	SOY Prot: 16% of E P/S: 0.44 Chol: 161 mg	
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	Crossover; random assignment; no run-in or washout periods	BASE Tot-C ND			
Giovannetti et al. (1986) (Ref. 36)	CON-1: 4 wk conventional food, moderate fat (38% of E); mixed protein sources	CON-1: 12 young adults, 20-28 yr, normal cholesterol levels	CON-1: mixed sources	CON-1 Prot: 18% of E Sat fat: NR Chol: NR	SOY-1 v. CON-1 Tot-C: -4 mg/dL (NS) LDL-C: -6 mg/dL (NS) HDL-C: -3 mg/dL (NS)
	SOY-1: 4 wk conventional food; moderate fat (38% of E); meat replaced by soy analogs and milk replaced by soy beverage (88% of total protein)	SOY-1: same as above	SOY-1: 66-80 g (est) as ISP and other vegetable sources	SOY-1 Prot: 18% of E Sat fat: NR* Chol: NR**	
	CON-2: 4 wk conventional food, low fat (23% of E); mixed protein sources	CON-2: same as above	CON-2: mixed sources	CON-2 Prot: 18% of E Sat fat: NR* Chol: NR**	SOY-2 v. CON-2 Tot-C: +1 mg/dL (NS) LDL-C: -5 mg/dL (NS) HDL-C: +2 mg/dL (NS)
	SOY-2: 4 wk conventional food; low fat (23% of E); meat replaced by soy analogs and milk replaced by soy beverage (88% of total protein)	SOY-2: same as above	SOY-2: 66-80 g (est) as ISP and other vegetable sources	SOY-2 Prot: 18% of E Sat fat: NR* Chol: NR**	
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	Crossover; Latin square design	BASE Tot-C = 145 mg/dL		* P/S=1.24 ** 103-138 mg	No weight loss; LDL-C lower on soy diets for almost all subjects

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dL - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Van Raaij et al. (1981) (Ref. 58)	CON: 4 wk "typical Western" moderate fat (~38% of E) diet; 65% of total protein from casein in various foods and beverages	CON: 25 young adults, 18-28 yr	CON: casein and other sources	CON Prot: 24% of E Sat fat: 13.2% of E Chol: 387 mg	CON v. SOY-1 (BASE) Tot-C: -3 mg/dL (NS) LDL-C: -0.4 mg/dL (NS) HDL-C: +2.3 mg/dL (NS)
	SOY-1: 4 wk "typical Western" moderate fat (~38% of E) diet; 65% of total protein from a 2:1 mixture of casein and soy protein in various foods and beverages	SOY-1: 20 as above	SOY-1: 17 g (est) as ISP, casein and other sources	SOY-1 Prot: 24% of E Sat fat: 13.8% of E Chol: 398 mg	SOY-2 v. SOY-1 (BASE) Tot-C: -3 mg/dL (NS) LDL-C: -6.6 mg/dL (and sig diff from change for CON) HDL-C: +5.8 mg/dL
	SOY-2: 4 wk "typical Western" moderate fat (~38% of E) diet; 65% of total protein from soy protein in various foods and beverages	SOY-2: 24 as above	SOY-2: 54 g (est) as ISP and other sources	SOY-2 Prot: 24% of E Sat fat: 12.9% of E Chol: 365 mg	
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	Parallel design; 3 groups; 1.5 wk run-in on SOY-1(BASE) then CON, SOY-1, or SOY-2	BASE Tot-C = ~150 mg/dL			
Van Raaij et al. (1982) (Ref. 59)	CON: 4 wk "typical Western" moderate fat (34.5% of E) diet; 60% of total protein from casein	CON: 17 adults, 29-60 yr	CON: casein and other sources	CON Prot: 15.9% of E Sat fat: 15.3% of E Chol: 374 mg	SOY-1 v. CON-1 (BASE) Tot-C: -7.7 mg/dL (NS, but sig diff from SOY-2) LDL-C: -3.7 mg/dL (NS, but sig diff from SOY-2) HDL-C: +1.3 mg/dL (NS, but sig diff from CON-2)
	SOY-1: 4 wk "typical Western" moderate fat (34.5% of E) diet; 60% of total protein from soy protein isolate	SOY-1: 20 as above	SOY-1: 55 g as ISP and other sources	SOY-1 Prot: 16.2% of E Sat fat: 15.0% of E Chol: 381 mg	SOY-2 v. CON-1 (BASE) Tot-C: +1.2 mg/dL (NS) LDL-C: +7.6 mg/dL (NS) HDL-C: -1.7 mg/dl (NS)
	SOY-2: 4 wk "typical Western" moderate fat (34.5% of E) diet; 60% of total protein from soy protein concentrate	SOY-2: 20 as above	SOY-2: 55 g as SPC and other sources	SOY-2 Prot: 16.1% of E Sat fat: 14.9% of E Chol: 382 mg	
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	Parallel design; 3 groups; 2.5 wk run-in on CON –1 (BASE), then CON-2, SOY-1, or SOY-2	BASE Tot-C = 215 mg/dL; range 135-305 mg/dL		Dietary fiber CON< SOY-1<SOY-2	Greater decrease in serum lipids in subjects with weight loss >3 kg

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dl - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Jenkins et al., 1989 (Ref. 43)	CON-1: 4 wk conventional food reducing diet (1000 kcal); ~30% of E from fat	CON-1: 11 obese women, aged 23-56 yr	CON-1: mixed sources	CON-1 Prot: 55g Sat fat: NR Chol: 408 mg P/S: 0.25	CON-1 vs. BASE Tot-C: -12 mg/dL (NS) LDL-C: -13 mg/dL (NS) HDL-C: NS
	SOY: 4 wk conventional food reducing diet (1000 kcal as above) with 2 meals/d replaced by soy supplement drink; ~30% of E from fat	SOY: same as above	SOY: 17 g as ISP and SF plus other mixed sources	SOY Prot: 72 g Sat fat: NR Chol: 214 mg P/S: 0.32	SOY vs. BASE Tot-C: -22 mg/dL or –10% LDL-C: -20 mg/dL or –17% HDL-C: NS
	CON-2: 4 wk conventional food reducing diet (1000 kcal as above) with 2 meals/d replaced by milk supplement drink; ~30% of E from fat	CON-2: same as above	CON-2: 18 g as milk protein isolate and non-fat dried milk, plus other mixed sources	CON-2 Prot: 71 g Sat fat: NR Chol: 195 mg P/S: 0.30	CON-2 vs. BASE Tot-C: -14 mg/dL (NS) LDL-C: -12 mg/dL (NS) HDL-C: -3 mg/dL (NS)
	---- Randomized, crossover for two periods (CON-1 and SOY), then all CON-2	----- Base Tot-C = 197 mg/dL	-----	-----	----- Weight loss not significantly different on different diets
Bosello et al., 1988 (Ref. 29)	CON: 15 days very low calorie (375 kcal) commercial preparation with casein; then 60 days adding integrating diet of conventional foods for hypocaloric regimen (800 kcal total)	CON: 12 obese adults, 25-42 yr (6 male)	CON: 27 g as casein, plus other mixed sources	CON Prot: 47 g Sat fat: ~2 g Chol: NR P/S: 0.44	CON vs. BASE Tot-C: -15 mg/dL or -7% (NS) LDL-C: -8 mg/dL or -5% HDL-C: -9 mg/dL or -16%
	SOY: 15 days very low calorie (375 kcal) commercial preparation with soy protein; then 60 days adding integrating diet of conventional foods for hypocaloric regimen (800 kcal total)	SOY: 12 as above	SOY: 28 g as SF(?)	SOY Prot: 47 g Sat fat: ~2 g Chol: NR P/S: 0.44	SOY vs. BASE Tot-C: -35 mg/dL or -16% LDL-C: -24 mg/dL or -15% HDL-C: -4 mg/dl or -7% (NS)
	----- Parallel design; 7 day run-in with isocaloric standard diet	----- Base Tot-C: 215 mg/dL for CON; 219 mg/dL for SOY	-----	-----	----- Body weight loss was the same on the two diet

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dl - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Sacks et al. 1983 (Ref. 53)	CON: 3 wk usual macrobiotic vegetarian diet with casein supplement	CON: 13 strict vegetarians, 21-40 yr (9 male)	CON: 27 g casein	BASE Prot: 59 g Sat fat: 5 g Chol: 12 mg	CON vs. BASE Tot-C: -4 mg/dL (NS) LDL-C: -1 mg/dL (NS) HDL-C: +1 mg/dL (NS)
	SOY: 3 wk usual macrobiotic vegetarian diet with soy protein supplement	SOY: same as above	SOY: 27 g as ISP	CON and SOY Prot: 82 g Sat fat: 5 g Chol: 30 mg	SOY vs. BASE Tot-C: -3 mg/dL (NS) LDL-C: -1 mg/dL (NS) HDL-C: + 2mg/dL (NS) SOY vs. CON Tot-C: NS LDL-C: NS HDL-C: NS
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	Crossover design	BASE Tot-C = 129 mg/dL			

Table 1. Summary of Clinical Trials: Subjects with Total Cholesterol Levels <300 mg/dl - continued

Acronyms and Abbreviations Used in Table

BASE	baseline
Chol	dietary cholesterol
CON	control diet
d	day
dL	deciliter
E	energy
est	estimated
g	gram
HDL-C	serum high density lipoprotein cholesterol level
ISP	isolated soy protein
Kcal	kilocalorie
LDL-C	serum low density lipoprotein cholesterol level
mg	milligram
mon	month
NCEP	National Cholesterol Education Program
NR	not recorded
NS	not statistically significant*
Prot	dietary protein
P/S	polyunsaturated to saturated fat ratio
Sat fat	saturated far
SF	soy flour
sig diff	statistically significant difference
SPC	soy protein concentrate
SOY	soy-containing diet
Tot-C	serum total cholesterol level
TVP	textured vegetable protein
wk	week
yr	year

* Results are statistically significantly different unless noted otherwise

Table 2. Studies of Subjects with Type II or Familial Hypercholesterolemia

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Sirtori et al. (1977) (Ref. 55)	CON: 3 wk low-lipid (21% of E) with total protein comprising 62% animal and 38% vegetable sources	CON: 20 adults with type-II hypercholesterolemia (? male); age NR	CON: mixed protein sources	CON Prot: 21% Sat fat: 4.3% of E Chol: *	CON v. BASE (2 periods) Tot-C: -18 (NS) & +23 mg/dL LDL-C: -19(NS) & +12 mg/dL (NS) HDL-C: NR
	SOY: 3 wk low-lipid (26% of E) with total protein comprising 63% soy, 30% other vegetable, and 7% animal sources	SOY: same as above	SOY: 60 g (est) as ISP (in TVP)	SOY Prot: 21% of E Sat fat: 4.3% of E Chol: 0-6 mg	SOY v. BASE (2 periods) Tot-C: -60 & -77 mg/dL LDL-C: -36 & -56 mg/dL HDL-C: NR
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	Crossover; metabolic ward; random assignment to SOY or CON initially; 1-wk run-in on usual diet in hospital; no washout between test diets	BASE Tot-C = ~333 mg/dL	Details about diets NR	Note: Chol intake * 100 mg/1,000 kcal	Comparison of SOY v. CON NR
Descovich et al. (1980) (Ref. 33)	CON: 8 wk standardized usual therapeutic diet; 20% of total protein from vegetable sources; moderately hypocaloric	CON: 127 adults, mean age 50 yr (67 male)	CON: mixed protein sources	CON Prot: 20% of E Sat fat: NR P/S: 1.8-2.0	CON v. BASE Tot-C: -2.8% (NS) LDL-C: NR (NS) HDL-C: NS
	SOY: 8 wk usual diet with soy analogs substituted for most animal proteins; 90% of total protein from vegetable sources	SOY: same as above	SOY: 31-62 g as SF (in TVP)	SOY Prot: 19% of E Sat fat: NR P/S: 18-2.3	SOY v. first CON Tot-C: -24% LDL-C: -31% HDL-C: NS
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	Fixed sequence: CON—SOY—CON	BASE Tot-C = 351 mg/dL		Chol: NR	NS weight loss
Wolfe et al. (1981) (Ref. 64)	CON: 6-8 wk low-cholesterol diet of conventional foods	CON: 7 adults with hyper-cholesterolemia, 29-60 yr, (? male)	CON: mixed protein sources (77 g)	CON Prot: 15% of E Sat fat: ~10% of E Chol: 88 mg	
	SOY: 6-8 wk low-cholesterol diet with soy analogs substituted for meats and cow milk	SOY: same as above	SOY: 47 g as ISP, with other vegetable protein	SOY Prot: 15% of E Sat fat: ~10% of E Chol: 88 mg	SOY v. CON Tot-C: -41 mg/dL LDL-C: -43 mg/dL HDL-C: +1 mg/dL (NS)
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	Crossover; random assignment to CON or SOY initially; no run-in or washout	BASE Tot-C NR			No weight change on diets

Table 2. Studies of Subjects with Type II or Familial Hypercholesterolemia - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Sirtori et al. (1985) (Ref. 56)	CON: 4 wk low-lipid (25% of E) with total protein comprising 60% animal and 40% vegetable sources	CON: 65 adults with type IIa hypercholesterolemia, 20-69 yr, (29 male)	CON: mixed protein sources	CON Prot: 20% of E Sat fat: NR Chol: 140-180 mg	CON v. BASE Tot-C: -4.7% (NS) LDL-C: NS HDL-C: NS
	SOY-1: 4 wk low-lipid (25% of E) with soy replacing most of animal protein for total protein comprising 10% animal and 90% vegetable sources	SOY-1: same as above	SOY-1: 60 g (est) as SF (in TVP)	SOY-1 Prot: 20 % of E Sat fat: NR Chol: 20-60 mg	SOY-1 v. first CON Tot-C: -19% LDL-C: -23% HDL-C: +8%
	SOY-2: 4 wk low-lipid (25% of E) with soy replacing much of animal protein for total protein comprising 30% animal and 70% vegetable sources	SOY-2: same as above	SOY-2: 30 g (est) as SF (in TVP)	SOY-2 Prot: 20 % of E Sat fat: NR Chol: 80-120 mg	SOY-2 v. first CON Tot-C: -13% LDL-C: -18% HDL-C: +8%
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	Fixed sequence: CON—SOY-1—CON—SOY-2; 45-d run-in on low-lipid diet	BASE Tot-C = 364 mg/dL		P:S ratio balanced across diets	
Verrillo et al. (1985) (Ref. 60)	CON: 8 wk low-fat (~33% of E) mixed-protein diet; 60% of total protein from animal sources	CON: 66 adults with familial or type II hypercholesterolemia, mean age 50 yrs (29 male)	CON: mixed protein sources	CON Prot: 17% of E Sat fat: 7 % of E Chol: ~200 mg	
	SOY-1: 16 wk low-fat (34% of E) with soy substituted for most of animal protein sources	SOY-1: 20 of above	SOY-1: 31 g as SF (in TVP)	SOY-1 Prot: 15% of E Sat fat: 7% of E Chol: 188 mg	SOY-1 v. mean of CON diets Tot-C: -29.5% LDL-C: -38.0% HDL-C: +7.7% (NS)
	SOY-2: 16 wk low fat (31% of E) with a supplement of soy protein added	SOY-2: 41 of above	SOY-2: 31 g as SF (in TVP)	SOY-2 Prot: 20% of E Sat fat: 7 % of E Chol: 205 mg	SOY-2 v. mean of CON diets Tot-C: -29.9% LDL-C: -36.5% HDL-C: -7.1% (NS)
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	Fixed-sequence: CON—(Soy-1 or Soy-2)—CON	BASE Tot-C = ~309 mg/dL			Difference between SOY-1 and Soy-2 NS

Table 2. Studies of Subjects with Type II or Familial Hypercholesterolemia - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Lovati et al. (1987) (Ref. 46)	CON: 4 wk low-lipid (26% of E from fat) with animal protein	CON: 12 adults with hyper-cholesterolemia, 26-64 yr (5 male)	CON: mainly animal protein; details NR	CON Prot: 20% of E P/S: ~2.0 Chol: 150 mg	CON v. BASE Tot-C: NR (NS) LDL-C: NR (NS) HDL-C: NR (NS)
	SOY: 4 wk same diet as CON with soy products substituted for all animal protein	SOY: same as above	SOY: ~70-105 g as SF (in TVP); details NR	SOY Prot: 20% of E P/S: ~2.0 Chol: 150 mg	SOY v. BASE Tot-C: -18% & –14% (for each of two sequences) LDL-C: -16% (average of both sequences) HDL-C: NR (NS)
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	Crossover; random assignment to CON or SOY initially; 1-month run-in on diet with animal protein and P/S ~2.0; 3-4 wk washout between test diets	BASE Tot-C = 410 mg/dL (range 305-600 mg/dL)			Note: SOY v. CON NR
Gaddi et al. (1991) (Ref. 35)	CON: 4 wk controlled low-lipid diet; 40% of total protein from vegetable sources	CON: 21 adults with familial hypercholesterolemia, 20-60 yr (8 male)	CON: mixed protein sources	CON Prot: 20% of E Sat fat: 6.5% of E Chol: 120-250 mg	CON v. BASE Tot-C: -11 mg/dL (NS) LDL-C: -16 mg/dL (NS) HDL-C: NS
	SOY: 4 wk low-lipid diet with soy analogs substituted for all animal proteins; 100% of protein from vegetable sources (75% of that from soy)	SOY: Same as above	SOY: 75 g as SF (in TVP)	SOY Prot: 20% of E Sat fat: 6.5% of E Chol: <10 mg	SOY v. first CON Tot-C: -82 mg/dL LDL-C: -79 mg/dL HDL-C: NS
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	Fixed sequence: CON—SOY—CON	BASE Tot-C = 402 mg/dL	-----	-----	-----
				Note: Chol intake	
Gaddi et al. (1987) (Ref. 34)	CON: 4 wk low-lipid (25% of E) therapeutic diet; total protein comprising 70% animal and 30% vegetable sources	CON: 16 children with familial hypercholesterolemia, 3-12 yr	CON: mixed protein sources	CON Prot: 20% of E Sat fat: NR Chol: NR	CON v. BASE Tot-C: -14 mg/dL (NS) LDL-C: -10 mg/dL (NS) HDL-C: NS
	SOY: 18 wk low lipid (25% of E) diet like CON with soy substituted for most of the animal products; total protein 10% animal and 90% vegetable sources	SOY: 12 of above	SOY: ? g as SF (in TVP) actual amount NR	SOY Prot: 20% of E Sat fat: NR Chol: NR	SOY v. CON Tot-C: -73 mg/dL LDL-C: -73 mg/dL HDL-C: NS
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	Fixed Sequence: CON—SOY	BASE Tot-C = 376 mg/dL			

Table 2. Studies of Subjects with Type II or Familial Hypercholesterolemia - continued

Study	Duration and Type of Control (CON) and Soy Protein (SOY) Dietary Treatments	Subject Numbers and Characteristics	Protein Sources and Amounts of Soy Protein	Dietary Intakes	Results
Widhalm et al. (1993) (Ref. 63)	CON: 8 wk low-fat (35% of E) diet; mixed protein sources	CON: 23 children with familial or polygenic hypercholesterolemia, mean age = 9.3 yr	CON: mixed sources	CON Prot: 15% of E P/S: 0.65 Chol: 190mg	CON (I & II) v. BASE Tot-C: -18% (NS) & -12% LDL-C: -7% (NS) &-13% HDL-C: -5% (NS) & +1% (NS)
	SOY: 8 wk low-fat (32% of E) diet enriched with a soy supplement	SOY: same as above	SOY: 14-18 g as SF	SOY Prot: 18% P/S: 0.73 Chol: 140 mg	SOY (I & II) v. BASE Tot-C: -16% & -18% LDL-C: -22% & -25% HDL-C: -1% (NS) & -13% (NS)
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	Crossover; Group I fed SOY initially and Group II fed CON initially; 8 wk washout with usual diet between test diets	BASE Tot-C > 90th percentile			Comparison of SOY v. CON NR
Laurin et al. (1991) (Ref. 45) and Jacques et al. (1992) (Ref. 42)	CON: 4 wk low-lipid (28% of E) diet; mixed protein sources including cow milk	CON: 10 children with familial hypercholesterolemia, 6-12 yr	CON: milk and other protein sources	CON Prot: 19% of E Sat fat: NR Chol: 181 mg	CON v. BASE* Tot-C: +10 mg/dL (NS) LDL-C: -8 mg/dL (NS) HDL-C: +1 mg/DL (NS)
	SOY: 4 wk low-lipid (28% of E) diet; soy beverage substituted for cow milk, with other components held constant	SOY: same a above	SOY: 28 g as ISP; other protein sources	SOY Prot: 20% of E Sat fat: NR Chol: 163	SOY v. BASE* Tot-C: -2 mg/dL (NS) LDL-C: -0.4 mg/dL (NS) HDL-C: +4 mg/dL (NS) SOY v. CON** Tot-C: 0 (NS) LDL-C: +2 mg/dL (NS) HDL-C: +2 mg/dL
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	Crossover; random assignment to SOY or CON initially; run-in with usual diet regimen (BASE); 4-wk washout with usual diet between test diets	BASE Tot-C range: 233-378 mg/dL		P:M:S = 1:3:3 in both test diets	* From Ref. 45 for n=9 ** From Ref. 42 for n=10

Table 2. Studies of Subjects with Type II or Familial Hypercholesterolemia - continued

Acronyms and Abbreviations Used in Table

BASE	baseline
Chol	dietary cholesterol
CON	control diet
d	day
dL	deciliter
E	energy
est	estimated
g	gram
HDL-C	serum high density lipoprotein cholesterol level
ISP	isolated soy protein
kcal	kilocalorie
LDL-C	serum low density lipoprotein cholesterol level
mg	milligram
mon	month
NR	not recorded
NS	not statistically significant*
Prot	dietary protein
P/S	polyunsaturated to saturated fat ratio
P:M:S	polyunsaturated to monounsaturated to saturated fat ratio
Sat fat	saturated far
SF	soy flour
sig diff	statistically significant difference
SPC	soy protein concentrate
SOY	soy-containing diet
Tot-C	serum total cholesterol level
TVP	textured vegetable protein
wk	week
yr	year

* Results are statistically significantly different unless noted otherwise

[FR Doc. 98–30008 Filed 11–9–98; 8:45 am]

BILLING CODE 4160–01–C