Proposed Rules

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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF ENERGY

10 CFR Parts 429 and 431

[EERE–2017–BT–TP–0055]

Energy Conservation Program: Test Procedure for Distribution Transformers

AGENCY: Office of Energy Efficiency and Renewable Energy, Department of Energy.

ACTION: Request for information; re-opening of public comment period.

SUMMARY: On September 22, 2017, the U.S. Department of Energy (DOE) published a request for information (RFI) pertaining to the test procedures for distribution transformers. The RFI provided an opportunity for submitting written comments, data, and information by October 23, 2017. This document announces that the period for submitting comments on the RFI is to be re-opened until November 6, 2017.

DATES: The comment period for the RFI, published on September 22, 2017 (82 FR 44347), is re-opened until November 6, 2017. DOE will accept written comments, data, and information in response to the RFI received no later than November 6, 2017.

ADDRESSES: Interested persons are encouraged to submit comments by any of the following methods:

- *Federal eRulemaking Portal: www.regulations.gov.* Follow the instructions for submitting comments.
- *Email: DistributionTransformers2017TP055@ee.doe.gov.* Include docket number EERE–2017–BT–TP–0055 in the subject line of the message. Submit electronic comments in WordPerfect, Microsoft Word, PDF, or ASCII file format, and avoid the use of special characters or any form of encryption.
- *Postal Mail:* Appliance and Equipment Standards Program, U.S. Department of Energy, Building Technologies Office, Mailstop EE–5B, 1000 Independence Avenue SW., Washington, DC 20585–0121. If possible, please submit all items on a compact disc (CD), in which case it is not necessary to include printed copies.
- *Hand Delivery/Courier:* Appliance and Equipment Standards Program, U.S. Department of Energy, Building Technologies Office, 950 L'Enfant Plaza SW., 6th Floor, Washington, DC 20024. Telephone: (202) 287–1445. If possible, please submit all items on a CD, in which case it is not necessary to include printed copies.

No telefacsimilies (faxes) will be accepted. For detailed instructions on submitting comments and additional information on the rulemaking process, see section III of the RFI published on September 22, 2017.

Docket: The docket for this activity, which includes **Federal Register** notices, comments, and other supporting documents/materials, is available for review at *http://www.regulations.gov.* All documents in the docket are listed in the *http://www.regulations.gov* index. However, some documents listed in the index, such as those containing information that is exempt from public disclosure, may not be publicly available.

The docket Web page can be found at *http://www.regulations.gov/#!docketDetail;D=EERE-2017-BT-TP-0055.* The docket Web page will contain simple instructions on how to access all documents, including public comments, in the docket.

FOR FURTHER INFORMATION CONTACT:

Mr. Jeremy Dommu, U.S. Department of Energy, Office of Energy Efficiency and Renewable Energy, Building Technologies Program, EE–5B 1000 Independence Avenue SW., Washington, DC 20585–0121. Telephone: (202) 586–9870. Email: *ApplianceStandardsQuestions@ee.doe.gov.*

Mary Greene, U.S. Department of Energy, Office of the General Counsel, GC–33, 1000 Independence Avenue SW., Washington, DC 20585–0121. Telephone: (202) 586–1817. Email: *mary.greene@hq.doe.gov.*

For further information on how to submit a comment, review other public comments and the docket, contact the Appliance and Equipment Standards Program staff at (202) 287–1445 or by email: *ApplianceStandardsQuestions@ee.doe.gov.*

SUPPLEMENTARY INFORMATION: DOE published a RFI pertaining to the test procedure for distribution transformers on September 22, 2017. 82 FR 44347. The RFI initiated a data collection process to consider whether to amend DOE's test procedures for distribution transformers. DOE requested written comment, data, and information pertaining to these test procedures by October 23, 2017.

The National Electrical Manufacturers Association (NEMA), an interested party in the matter, requested a two-week extension of the public comment period for the RFI published in the **Federal Register** on October 5, 2017. (NEMA, No. 4, at p. 1)

DOE believes that re-opening the comment period to allow additional time for interested parties to submit comments is appropriate. Therefore, DOE is re-opening the comment period until November 6, 2017 to provide interested parties additional time to prepare and submit comments. Comments received between the original October 23 closing date and the new November 6 closing date are considered timely filed. Therefore, individuals who submitted late comments during the original comment period do not need to re-submit comments.

Issued in Washington, DC, on October 19, 2017.

David Nemtzow,

Director, Building Technologies Office, Energy Efficiency and Renewable Energy.

[FR Doc. 2017–23635 Filed 10–30–17; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. FDA–2017–N–0763]

RIN 0910–AH43

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, the Agency, or we) is proposing to revoke its regulation authorizing the use of health claims on

the relationship between soy protein and coronary heart disease on the label or in the labeling of foods. We are taking this action based on our review of the totality of publicly available scientific evidence currently available and our tentative conclusion that such evidence does not support our previous determination that there is significant scientific agreement (SSA) among qualified experts for a health claim regarding the relationship between soy protein and reduced risk of coronary heart disease.

DATES: Submit either electronic or written comments on the proposed rule by January 16, 2018.

ADDRESSES: You may submit comments as follows. Late, untimely filed comments will not be considered. Electronic comments must be submitted on or before January 16, 2018. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of January 16, 2018. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2017–N–0763 for ''Food Labeling: Health Claims; Soy Protein and Coronary Heart Disease.'' Received comments, those received in a timely manner (see **DATES** and **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Crystal Rivers, Center for Food Safety and Applied Nutrition (HFS–830), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–1444.

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

The proposed rule would revoke the regulation authorizing the use of a health claim regarding the relationship between soy protein and risk of coronary heart disease (CHD) (§ 101.82 (21 CFR 101.82)). In this proposed rule, we tentatively conclude, based on our reevaluation of the totality of the publicly available scientific evidence now available, that the evidence does not support our previous determination that there is SSA to support an authorized health claim for the relationship between soy protein and reduced risk of CHD.

In 1999, we authorized a health claim about the relationship between soy protein and a reduced risk of CHD (§ 101.82). In the **Federal Register** of December 21, 2007, we announced our intention to reevaluate the scientific evidence for this health claim and provided the opportunity for public comment (72 FR 72738). We explained that we were reevaluating the scientific basis for the soy protein and CHD health claim because new studies yielded

varied and inconsistent findings (beneficial effect, no effect) from one trial to another. The results of these studies called into question the conclusions drawn from our prior review, which had served as the basis for authorizing the soy protein and reduced risk of CHD health claim. This proposed rule is the next step in our reevaluation.

B. Summary of the Major Provisions of the Proposed Rule

The proposed rule would revoke the soy protein and CHD claim in § 101.82 because it does not meet the SSA standard. Our decision about whether to authorize a health claim represents FDA's determination as to whether there is ''significant scientific agreement'' among qualified experts that the publicly available scientific evidence supports the substance/disease relationship that is the subject of a proposed health claim. In our reevaluation of the scientific evidence in this proposed rule, we use our approach outlined in the ''Evidence-Based Review System for the Scientific Evaluation of Health Claims'' (hereinafter the 2009 guidance) to evaluate the totality of publicly available scientific evidence to determine if the SSA standard in section 403(r)(3) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. (343(r)(3)) is met (Ref. 1). Our reevaluation of the totality of the publicly available scientific evidence indicates that, although some evidence suggests a relationship between soy protein intake and reduced risk of CHD, the totality of the evidence is inconsistent and not conclusive. Therefore, we have tentatively determined that the strength of the totality of the publicly available data does not meet the SSA standard for a relationship between soy protein intake and CHD risk.

C. Costs and Benefits

The costs of this proposed rule, if finalized, are relabeling the estimated 200 to 300 products currently making the health claim. We estimate total annualized costs of $35,000 to $81,000, when the relabeling costs are annualized over 20 years at a 7 percent discount rate. The initial one-time costs are $370,000 to $860,000.

The benefit of this rule is better information for the consumers who are considering purchasing products with soy protein. This may generate an unknown amount of increased consumer surplus. Some consumers may react to this new information by switching their consumption to products that they enjoy more, or products that still have an authorized health claim. By basing their consumption decisions on more recent and accurate scientific information, they may get more consumer surplus, in the form of enjoyment and/or potential health benefits, from the bundle of products they consume.

TABLE 1—COST AND BENEFIT OVERVIEW, USD, ANNUALIZED OVER 20 YEARS

	Low estimate	Mean	High estimate
Costs, 7 percent discount rate	$35,000	$55,000	$81,000
Costs, 3 percent discount rate	$25,000	$39,000	$58,000
Benefits	Consumer Enjoyment and/or potential Health Benefits		

II. Table of Commonly Used Acronyms in This Document

TABLE 2—TABLE OF COMMONLY USED ACRONYMS

Acronym	What it means
CHD	Coronary Heart Disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
FDA	Food and Drug Administration
g	gram(s)
kcal	kilocalorie(s)
LDL	Low-Density Lipoprotein
mg	milligram(s)
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung and Blood Institute
oz	ounces
SBP	Systolic Blood Pressure
SSA	Significant Scientific Agreement
TC	Total Cholesterol

III. Background

In the **Federal Register** of November 10, 1998 (63 FR 62977), and in response to a petition from Protein Technologies International, Inc. (see Docket No. FDA–1998–P–1154), we proposed to provide for health claims on the relationship of soy protein and reduced risk of CHD (hereinafter referred to as the 1998 soy protein proposed rule). In the 1998 soy protein proposed rule, we considered the relevant scientific studies and data presented in the petition as part of our review of the scientific literature on soy protein and CHD. We summarized these studies in table 1 of the soy protein proposed rule (63 FR 62977 at 62998) and presented the rationale for a health claim on this food/disease relationship as provided for under the significant scientific agreement standard in section 403(r)(3)(B)(i) of the FD&C Act and § 101.14(c).

In our 1998 evaluation of the scientific evidence for a relationship between consumption of soy protein and blood total and LDL-cholesterol levels (two validated surrogate endpoints for risk of CHD), we found the data suggestive, but not sufficient, to establish a dose-response for this relationship. However, we found consistent, clinically significant reductions of total- and LDL-cholesterol levels in controlled trials that used at least 25 grams (g) of soy protein per day. Thus, we proposed to base the qualifying level of soy protein on a total daily intake of 25 g, as suggested by the petitioner. For the purposes of health claims, we assumed there are four eating occasions a day (*i.e.,* three main meals and one snack). Therefore, in § 101.82(c)(2)(iii)(A), we proposed the qualifying criterion for a food to bear the claim as 6.25 g of soy protein per reference amount customarily consumed (RACC) (*i.e.,* 25 g divided by four eating occasions per day).

In the **Federal Register** of October 26, 1999 (64 FR 57700), we authorized a health claim for soy protein and risk of coronary heart disease (21 CFR 101.82). As explained in the final rule, we determined, based on our review of evidence submitted with comments to the proposed rule, as well as evidence described in the proposed rule, that soy protein included in a diet low in saturated fat and cholesterol may reduce the risk of CHD by lowering blood cholesterol levels. FDA's requirements for use of the health claim and model health claim language were codified at 21 CFR 101.82.

FDA evaluates new scientific information that becomes available to determine whether it necessitates a change to an SSA health claim. On December 21, 2007, we published a notice in the **Federal Register** (72 FR 72738) (the 2007 reevaluation notice) announcing our intent to reevaluate the scientific evidence for certain health claims, including the authorized health claim for soy protein and risk of CHD (§ 101.82). We stated that we were reevaluating the scientific basis for the soy protein and CHD health claim because numerous studies published since we had authorized the health claim had evaluated the relationship between soy protein and CHD, and the findings of these studies were inconsistent from study to study. For example, the Agency for Healthcare Research and Quality (AHRQ) released a report in July 2005 outlining the effects of soy products on health outcomes, including cardiovascular disease, and concluded that soy products appear to exert a small benefit on LDL cholesterol (Ref. 2). However, the AHRQ report included studies that evaluated substances in addition to soy protein (*e.g.,* isolated soy isoflavones). It was not clear from the AHRQ report whether the soy protein, or other components of soy products such as isoflavones, were responsible for lowering LDL cholesterol. In addition, the AHRQ report used markers of cardiac function (*e.g.,* triglycerides, endothelial function, and oxidized low-density lipoprotein) that are not surrogate endpoints recognized by FDA for CHD risk.

Subsequently, we received a citizen petition dated August 8, 2008 (Docket Number FDA–2008–P–0452–001) (hereinafter ''the 2008 citizen petition''), requesting that the Commissioner of Food and Drugs revoke § 101.82. On January 4, 2016, we denied the petitioner's request because the limited relevant evidence submitted in the petition and a supplement to the petition did not provide sufficient grounds for us to revoke the soy protein and CHD health claim. However, as noted in the response to the citizen petition, we considered the relevant studies included in the petition as part of our reevaluation.

IV. Legal Authority

The Nutrition Labeling and Education Act of 1990 (NLEA) (Pub. L. 101–535) amended the FD&C Act by, among other things, adding section 403(r) to the FD&C Act. This section specifies, in part, that a food is misbranded if it bears a claim that expressly or by implication characterizes the relationship of a nutrient to a disease or health-related condition unless the claim is made in accordance with section 403(r)(3) of the FD&C Act (for conventional foods) or 403(r)(5)(D) of the FD&C Act (for dietary supplements).

The NLEA also directed FDA to issue regulations authorizing health claims (*i.e.,* labeling claims that characterize the relationship of a nutrient to a disease or health-related condition) for conventional foods if we determine, based upon the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner that is consistent with generally recognized scientific procedures and principles), that there is SSA, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence (see section 403(r)(3)(B)(i) of the FD&C Act). FDA may reevaluate the science related to an authorized health claim and may take action to revoke the claim (see section 403(r)(7)(B) of the FD&C Act (21 U.S.C. 343(r)(7(B)).

Additionally, our regulations, at 21 CFR 10.40(a), provide that we may promulgate regulations necessary to enforce the FD&C Act as appropriate and may initiate such action in any of the ways specified in § 10.25 (21 CFR 10.25). Specifically, § 10.25(b) provides that the Commissioner may initiate a proceeding to revoke a regulation. Accordingly, we are acting within our statutory and regulatory authorities to propose to revoke the authorized health claim for soy protein and a reduced risk of CHD. If this proposed rule is finalized, the use of an authorized health claim would be prohibited and a food that bears the health claim on the label or in labeling would misbrand the food (see section 403(r)(1)(B) of the FD&C Act).

In situations where we determine that the totality of the publicly available scientific evidence does not meet the statutory SSA standard, we may consider whether there is credible evidence to support a ''qualified'' health claim and what qualifying statements and other information should accompany the claim to ensure that it is truthful and not misleading. If, when we finalize this rule, we conclude there is not SSA, but there is some credible evidence for the use of a qualified health claim about the relationship between soy protein and a reduced risk of CHD, we intend to issue a statement of enforcement discretion for the use of a qualified health claim.

V. Scientific Evidence Regarding the Relationship Between Soy Protein and CHD

A. Overview of Data and Eligibility for a Health Claim

Health claims characterize the relationship between a substance and a reduction in risk of contracting a particular disease or developing a health-related condition (*Whitaker* v. *Thompson,* 353 F.3d 947, 950–51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), cert. denied, 125 S. Ct. 310 (2004)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup, is at risk (§ 101.14(b)(1)). We analyze the information and data related to a health claim under the framework set out in our 2009 guidance titled, ''Evidence-Based Review System for the Scientific Evaluation of Health Claims'' (Ref. 1). The 2009 guidance discussed our process for evaluating the scientific evidence for a health claim and the meaning of the significant scientific agreement (SSA) standard in section 403(r)(3) of the FD&C Act (21 U.S.C. 343(r)(3)) and 21 CFR 101.14(c). In a review of a health claim, our first step is to identify the substance, the disease or health-related condition that is the subject of the claim, and the population to which the claim is targeted (Ref. 1).

Next, we consider the totality of publicly available data and information to determine whether the scientific evidence could support a relationship between the substance and the disease or health-related condition. We begin this process by organizing the evidence into categories, such as human studies, meta-analyses, review articles, animal studies, and in vitro studies, so we can thoroughly and systematically assess the evidence during the evaluation process. Each category of evidence may offer us helpful information and a better understanding of the topic; however, only well-designed, well-conducted human studies provide both the level of scientific rigor and generalizability to human populations needed to potentially support a health claim relationship. We focus our review on reports of human intervention studies and observational studies. Of the two types of studies, well-conducted intervention studies provide the strongest evidence of an effect and are the most reliable category of studies for determining a cause-and-effect relationship (Ref. 1). In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the

intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (*i.e.,* disease). Observational studies lack the controlled setting of intervention studies. In contrast to intervention studies, observational studies cannot determine whether an observed relationship represents a relationship in which the substance caused a reduction in disease risk or if other factors or variables may have contributed to an outcome (Ref. 3). In addition to individual reports of human studies, we also consider other types of data and information such as meta-analyses, review articles, and animal and in vitro studies. These other types of data and information may be useful to help us understand the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles do not provide sufficient information on the individual studies reviewed in order for us to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents us from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. We must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. We use meta-analyses, review articles, and similar publications to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, we evaluate them individually.

We use animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary substances (Ref. 4). Further, the physiology of animals is different than that of humans. Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

We evaluate the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Ref. 5–6). Studies from which we cannot draw any scientific conclusions do not support the health claim relationship, and we eliminate such studies from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, we consider evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. The available scientific evidence should demonstrate that: (1) The mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased and healthy people. If such evidence is not available, then we cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance/disease relationship. Next, we rate the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (*e.g.,* use of a placebo-control group versus a non-placebo-control group), data collection (*e.g.,* type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (*e.g.,* disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (*e.g.,* age, smoker versus non-smoker) to evaluate factors such as selection bias and whether important information about the study subjects was gathered and reported. For example, if the scientific study adequately addressed all or most of the criteria related to study design, we would assign a high methodological quality rating to the study. We would assign moderate or low quality ratings based on the extent of the deficiencies or uncertainties in the quality criteria. As noted in our guidance (Evidence-Based Review System for the Scientific Evaluation of Health Claims), this quality rating is based on several factors related to study design, data collection, the quality of the statistical analysis, the type of outcome measured, and study population characteristics other than relevance to the U.S. population (*e.g.,* selection bias and the provision of important subject information [*e.g.,* age, smokers]). (Ref. 1). We would not use studies that are so deficient that scientific conclusions cannot be drawn from them to support the health claim relationship, and we eliminate such studies from further review.

We then evaluate the results of the remaining human studies and then rate the overall strength of the total body of publicly available evidence (Ref. 1). We consider the study type (*e.g.,* intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated (Ref. 7), and the overall consistency (Ref. 8–9) of the total body of evidence (Ref. 1). Based on the totality of the publicly available scientific evidence, we determine whether such evidence meets that SSA standard to support an authorized health claim (also referred to as ''SSA health claim'') for the substance/disease relationship. If the evidence does not meet the SSA standard, then we may consider whether such evidence is credible to support a qualified health claim. If there is credible evidence to support a qualified health claim, then we consider what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

B. Reevaluation of the Health Claim for Soy Protein Intake and CHD

In our reevaluation of the scientific evidence for a relationship between soy protein and reduced risk of CHD, we have used the approach outlined in the 2009 guidance to evaluate the totality of the current publicly available scientific evidence regarding this relationship (see section 403(r)(3)(B) of the FD&C Act). In this section, we present our reevaluation of the totality of the publicly available scientific evidence, including the studies we previously reviewed in promulgating the regulation that authorized the 1999 soy protein and CHD health claim (64 FR 57700), as well as studies published after we authorized the health claim in 1999. The 2009 guidance represents FDA's current

thinking on the evaluation of health claims as well as the interpretation and meaning of SSA. Because the 1999 final rule predates that guidance, we acknowledge that our reevaluation of studies previously considered in the 1999 rulemaking may differ in certain respects from the previous evaluation. For the purposes of this review, we have identified the following disease endpoints for use in identifying CHD risk reduction for the purposes of a health claim evaluation: The incidence of coronary events (*e.g.,* myocardial infarction, ischemia), cardiovascular death, coronary artery disease, atherosclerosis, and CHD (Ref. 1). We consider high blood pressure, blood (serum or plasma) total cholesterol (TC), and blood LDL cholesterol levels to be surrogate endpoints for CHD risk (Ref. 1). We use these disease and surrogate endpoints to evaluate the potential effects of soy protein on CHD risk.

For the purposes of the reevaluation, we identified a total of 709 publications, drawn from studies included in the 1999 final rule, comments submitted to the 2007 notice of reevaluation, the 2008 citizen petition, and searches of the more recent literature. These publications consisted of 30 in vitro studies; 85 animal studies; 27 government documents; 163 review articles, meta-analyses, letters, abstracts, and books or book chapters; 11 Web sites; 3 articles written in a foreign language; and 141 publications that did not evaluate the substance/disease relationship. The publications also included 11 observational studies that evaluated the substance/disease relationship and 238 publications describing intervention studies that evaluated the relationship between soy protein intake and CHD risk.

1. Assessment of Review Articles, Meta-Analyses, Book Chapters, Letters, and Government Reports

Although useful for background information, review articles, meta-analyses, book chapters, letters, and government reports do not contain sufficient information on the individual studies which they reviewed and, therefore, we could not draw any scientific conclusions from this information. For example, we could not determine factors such as the study population characteristics or the composition of the products used (*e.g.,* food, dietary supplements). Similarly, the lack of detailed information on studies summarized in review articles, meta-analyses, book chapters, letters, and government reports prevents us from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. We need to be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, while the review articles, meta-analyses, book chapters, letters, and government reports we identified provided useful background information, they did not provide sufficient information from which scientific conclusions could be drawn regarding soy protein consumption and risk of CHD.

2. Assessment of Animal and *In Vitro* Studies

We use animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease; these studies also can be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between a substance and a disease in humans (Ref. 1, 4). Such studies cannot mimic the normal human physiology that may be involved in the risk reduction of CHD, nor can the studies mimic the human body's response to the consumption of soy protein. Therefore, we cannot draw any scientific conclusions from the animal or *in vitro* studies regarding soy protein and the risk of CHD in humans, and they provide insufficient data to support a health claim. In accordance with these principles, in our review we considered animal and *in vitro* studies but determined that they did not provide useful supportive information about the relationship between soy protein consumption and risk of CHD.

C. Assessment of Intervention Studies

For the purposes of this review, we categorized the intervention studies based on whether the subjects: (1) Added soy protein to the diet (supplement) in addition to the subjects' usual diet; (2) were instructed to substitute soy protein for animal protein in their diet; and (3) were provided test diets (feeding studies) with soy protein for animal protein (usually casein) in the control diet. In studies where soy proteins were used as a substitute for animal proteins, changes in the total fat, saturated fat, cholesterol, and dietary fiber content of the diet can occur. A reduced intake of total fat (Ref. 10), saturated fat ((Ref. 10), or cholesterol (Ref. 11) has been shown to lower blood cholesterol, and an increased intake of dietary fiber (Ref. 12) has shown the same (Ref. 10), and we have authorized SSA health claims for reduced risk of CHD based on these substance and disease relationships (§ 101.75, § 101.81). Therefore, to determine the independent effect of soy protein intake on blood cholesterol levels, total fat, saturated fat, cholesterol, and dietary fiber need to be controlled for in the studies. Studies that substituted soy protein for animal protein or feeding studies that did not properly control for these nutrients and/or did not report these nutrients were eliminated from further review. For studies in which soy protein was added to the usual diet, the addition of soy protein should not result in significant changes in the total fat, saturated fat, cholesterol, and dietary fiber in the diet (because soy protein does not have significant amounts of these nutrients) (Ref. 13–15). Therefore, we did not eliminate these types of studies that did not control for and/or did not report these nutrients.

To determine the independent effects of soy protein on blood pressure, studies need to control for the amount of sodium and potassium, because both nutrients influence blood pressure (Ref. 16). Studies that substituted soy protein for animal protein or feeding studies where subjects were provided soy protein in test diets that did not properly control for these nutrients and/or did not report these nutrients were eliminated from further review. For studies that added soy protein to the diet, the addition of soy protein should not result in significant changes in the amount of sodium and potassium in the diet; therefore, we did not eliminate these types of studies that did not control for and/or did not report these nutrients (Ref. 13–15). Furthermore, because the nutrients that affect blood pressure (sodium and potassium) and cholesterol (saturated fat, dietary fiber, and cholesterol) are different, some studies might be appropriate for supporting one surrogate endpoint, but not the other. Thus, for the purposes of this assessment, we discuss some studies twice.

Of the 238 total publications describing intervention studies that evaluated the relationship between soy protein intake and CHD risk, 9 publications did not report data on a FDA-recognized surrogate endpoint of CHD risk (*i.e.,* blood total cholesterol, blood LDL cholesterol, blood pressure) (Ref. 17–25). Because these publications did not report data on one or more surrogate endpoints, we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from these studies (Ref. 1).

The remaining 229 publications described 212 intervention studies that evaluated soy protein intake and CHD

risk. Of these 212 intervention studies, scientific conclusions could not be drawn from 154 studies due to significant flaws. These studies are discussed in sections V.C. 1. and V.C. 2. Such studies may have other flaws in addition to those specifically mentioned. This left 58 well-designed, well-conducted intervention studies to include in our evaluation of the totality of the publicly available scientific evidence.

1. Intervention Studies That Examined Soy Protein Intake and Blood Cholesterol

As stated previously in this section, we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from 154 intervention studies due to significant design flaws. These studies include 17 studies that did not include a control group or provide an appropriate control for the comparison to the relative effects of soy protein (Ref. 26–42). Without an appropriate control group, we could not determine if the changes in LDL cholesterol were due to soy protein intake or uncontrolled extraneous factors (Ref. 1). Therefore, we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from these studies

Ten studies did not conduct statistical analyses between the control group and treatment group. The statistical analysis of the substance/disease relationship is a critical factor because it provides the comparison between subjects that consumed soy protein and those that did not consume soy protein (*i.e.,* control) to determine whether there is a reduction in CHD risk (Ref. 43–52). Therefore, we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from these studies.

In eight studies (Ref. 53–60), the duration of the study intervention was too short (less than 3 weeks) to adequately determine if changes in serum cholesterol levels were due to the consumption of soy protein (Ref. 1, 61). Therefore, we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from these studies.

Seventy-six studies, described in 84 publications, that substituted soy protein for animal protein or were feeding studies reported large differences in or did not report information on other dietary components that have an effect on blood cholesterol (*e.g.,* dietary fiber, saturated fat, dietary cholesterol) (Ref. 56, 62–145). Such large differences in nutrient intakes of dietary fiber, saturated fat, or dietary cholesterol make it difficult to clearly delineate what may be causing a change in serum cholesterol levels. Therefore, the results of these studies could not be interpreted, and we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from these studies (Ref. 1).

One study, Zittermann et al. (2004) was a randomized, crossover study (Ref. 1) in which 14 German women consumed 5 cookies made with soy flour or 5 cookies made with wheat flour while they remained on their usual diet for one menstrual cycle (30.8 ± 0.9 days). The composition of the test cookies and of the amount of soy protein in the cookies was not adequately described. Furthermore, while the study reported that subjects were to consume the cookies while they remained on their usual diet, the study reported significantly higher intake of dietary fiber ($P < 0.0001$) in the soy period (cookies made with soy flour) than in the control period. When an intervention study involves providing a whole food rather than a food component, the experimental and control diets should be similar enough that the relationship between the substance and disease can be evaluated (Ref. 1). Because the composition of the test cookies were not adequately described, it is not clear why there are differences in dietary fiber intake between the two groups. Thus, we could not draw scientific conclusions about the relationship between soy protein and CHD when the amounts of other substances that are known to affect the risk of CHD (*e.g.* dietary fiber) are different between the control and experimental diets (Ref. 1, 146).

Nine studies, described in 11 publications that evaluated soy protein intake and blood cholesterol, contained added phytosterols in the treatment group (Ref. 131–132, 147–155). We have an existing regulation for a SSA health claim for the relationship between plant sterol/stanol esters and reduced risk of CHD; however, because plant sterol/stanol esters can reduce blood cholesterol, it is not possible to clearly delineate what may be causing a change in serum cholesterol levels (Ref. 1). Therefore, the results of these studies could not be interpreted, and we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from these studies.

For the remaining 58 intervention studies from which we could draw scientific conclusions, we used the criteria established by the National Heart, Lung and Blood Institute (NHLBI) to sort studies that measured blood cholesterol into 3 categories: (1) Studies that had subjects with desirable or borderline blood cholesterol (TC <240 mg/dL or LDL-cholesterol less than 160 mg/dL); (2) studies that had subjects with high blood cholesterol (TC >240 or LDL cholesterol >160 mg/dL); and (3) studies that had some subjects with desirable or borderline cholesterol level and other subjects with high cholesterol levels (Ref. 156). Additionally, studies that measured blood pressure were sorted based on criteria established by NHLBI into three categories: (1) Normal (Systolic Blood Pressure (SBP) <120 mmHg or Diastolic Blood Pressure (DBP) <80 mmHg); (2) pre-hypertension (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg); and (3) hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) (Ref. 157–158). Studies were further sorted by whether the studies added (supplemented) soy protein to the diet, were feeding studies, or were substitution studies. Because some studies measured both blood cholesterol and blood pressure, we discussed these studies twice (see tables 4–8 in Ref. 230).

a. Studies in subjects with desirable or borderline cholesterol levels that added isolated soy protein to the diet.

Carmignani et al. (2014) was a 16-week, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 40 postmenopausal Brazilian women consumed daily 40 g/day placebo powder of maltrodextrin (n=20) or 40 g/day protein powder containing 24 g/day isolated soy protein (90 mg/day naturally occurring isoflavones) (n=20) in addition to their usual diet (Ref. 159). There was no significant difference in blood TC and LDL cholesterol between the soy protein group and the control group.

Liu et al. (2012) was a 6-month, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 120 postmenopausal Chinese women consumed daily 15 g/day milk protein plus 100 mg/day isoflavone supplement (control) (n=60) or 15 g/day isolated soy protein plus 100 mg/day isoflavone supplement (n=60) in addition to their usual diet (Ref. 160). There was no significant difference in the change in blood TC and LDL cholesterol between the milk protein and isoflavone group (control) and the soy protein and isoflavone group.

Santo et al. (2008) was a 28-day, randomized, double-blind, controlled parallel trial of moderate quality in

which 30 American men consumed: (1) 25 g/day isoflavone-poor soy protein isolate (1.9 mg/day isoflavones) (n=11); (2) 25 g/day isoflavone-rich soy protein isolate (97 mg/day naturally occurring isoflavones) (n=10); or (3) 25 g/day of milk protein (n=9) (control) mixed with a beverage of their choice in addition to their usual diet (Ref. 161). There were no significant differences in blood TC and LDL cholesterol between the two soy protein isolate treatment groups and the casein control group.

Evans et al. (2007) was a randomized, double-blind, placebo-controlled, crossover trial of moderate quality in which 22 postmenopausal American women consumed: (1) 25 g/day isolated soy protein plus 20 g/day soy lecithin; (2) 25 g/day isolated soy protein plus placebo lecithin; (3) placebo protein (50:50 calcium/sodium caseinate) and 20 g/day soy lecithin; and (4) double placebo (protein placebo and soy lecithin) in addition to their usual diet, for a duration of 4 weeks each (Ref. 162). There was no significant difference in blood TC and LDL cholesterol between the isolated soy protein plus soy lecithin and placebo protein plus soy lecithin treatment period (control). There was also no significant difference in blood TC and LDL between the isolated soy protein plus placebo lecithin and double placebo period (control).

Maesta et al. (2007) was a 16-week, randomized, single-blind, placebo-controlled, parallel trial of moderate quality in which 46 postmenopausal Brazilian women consumed: (1) 25 g/day isolated soy protein (n=10); (2) 25 g/day isolated soy protein, plus resistance exercise (n=14); (3) 25 g/day maltodextrin (control) (n=11); or (4) 25 g/day maltodextrin plus resistance exercise (n=11) (control) in addition to their usual diet (Ref. 163). There was no significant difference in blood TC and LDL cholesterol between the soy protein and control groups.

Kohno et al. (2006) was a two-part, randomized, double-blind, placebo-controlled, parallel trial of moderate quality (Ref. 164). In the first part of the trial, 126 Japanese men and women, in addition to their usual diet, consumed daily 5 g casein (control) (n=61) or 5 g of soybean β-conglycinin (storage protein component of soy protein isolate) in the form of a candy (n=65) for 12 weeks. There was no significant difference between the two diets for blood TC or LDL cholesterol. In the second part of the trial, 95 Japanese men and women consumed daily 5 g casein (n=50) or 5g soybean β-conglycinin (n=45) for 20 weeks. There was no significant difference between the two diets for blood TC or LDL cholesterol.

McVeigh et al. (2006) was a randomized, single-blind, controlled, crossover trial of moderate quality in which 35 Canadian men consumed 32 g/day soy protein isolate depleted of isoflavones (1.64 mg/day), 32 g/day soy protein isolate (62 mg/day isoflavones), or 32 g/day milk protein isolate for a duration of 57 days each (Ref. 165). There was no significant difference between blood TC and LDL cholesterol between the soy protein and casein groups.

Sagara et al. (2004) was a 5-week, randomized, double-blind, placebo-controlled parallel trial of moderate quality in which 50 Scottish men consumed 20 g/day of isolated soy protein powder in biscuits, cereal bars, and bread rolls (n=25) or biscuits, cereal bars, and bread rolls without added soy protein in addition to their usual diets (n=25) (Ref. 166). There was no significant difference in blood TC between the two groups.

Teixeira et al. (2004) was a randomized, controlled, crossover trial of moderate quality in which 14 men American men with type 2 diabetes with nephropathy consumed an estimated 35 g/day of soy protein isolate and casein (control) in addition to their usual diets for a duration of 8 weeks each (Ref. 167). There was no significant difference in blood TC and LDL cholesterol between the soy protein and casein group.

Murray et al. (2003) was a 6-month, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 30 American postmenopausal women consumed: (1) 38 g/day soy protein isolate containing (25 g soy protein) plus 1.0 mg estradiol (n=8); (2) 38 g textured milk protein plus 1.0 mg estradiol (n=7) (control); (3) 38 g/day soy protein isolate containing (25 g soy protein) plus 0.5 mg estradiol (n=8); or (4) 38 g/day textured milk protein plus 0.5 mg estradiol(control) (n=7) in addition to their usual diet (Ref. 168). The baseline TC levels in the 38 g/day textured milk protein plus 1.0 mg estradiol group were significantly higher than the (25 g soy protein) plus 1.0 mg estradiol group. If the baseline cholesterol values between groups are significantly different, then it is difficult to determine if differences at the end of the study were due to the intervention or to differences observed at the beginning of the study (Ref. 1). Thus, we could not draw scientific conclusions from this arm of the study. For the soy protein group plus 0.5 mg estradiol and the textured milk protein plus 0.5 mg estradiol (control) groups, the baseline cholesterol levels were similar and conclusions could be drawn. However, there was no significant difference in blood TC and LDL cholesterol between the soy protein group plus 0.5 mg estradiol and the textured milk protein plus 0.5 mg estradiol control group.

Jayagopal et al. (2002) was a randomized, double-blind, placebo-controlled, crossover trial of moderate quality in which 32 postmenopausal British women with type 2 diabetes consumed 30 g/day of isolated soy protein or 30 g/day of cellulose (control) in addition to their usual diet for a duration of 12 weeks each (Ref. 169). Blood TC and LDL cholesterol was significantly lower ($P < 0.05$) in soy protein period compared to the cellulose period.

Higashi et al. (2001) (trial one) was a randomized, controlled, crossover trial of moderate quality in which 14 Japanese men consumed daily milk or yogurt only (no placebo) and 20 g/day soy protein isolate mixed in milk or yogurt in addition to their usual diet for a duration of 4 weeks each (Ref. 26). There was no significant difference in blood TC and LDL cholesterol between the soy protein period and the control period (milk or yogurt only).

Teede et al. (2001) and Dalais et al., (2003) was a 3-month randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 179 Australian men and postmenopausal women consumed a casein placebo (n=93) or 40 g/day soy protein isolate (n=86) mixed with a beverage twice a day in addition to their usual diet (Ref. 170–171). There was no significant difference in blood TC and LDL cholesterol between the casein control group and soy protein isolate group. In a subgroup analysis of the postmenopausal women (n=55 casein and n=51 soy protein) by Dalais et al. (2003), there was no significant difference in blood TC between the casein control group and soy protein isolate group. However, blood LDL cholesterol was significantly ($P < 0.05$) lower in the soy protein isolate group compared to the casein control group.

Washburn et al. (1999) was a randomized, double-blind, placebo-controlled, crossover trial of moderate quality in which 42 perimenopausal American women consumed daily: (1) 20 g/day complex carbohydrate supplement mixed with a beverage (control); (2) 20 g/day isolated soy protein (34 mg/day naturally occurring phytoestrogens) supplement mixed with a beverage as a single dose; and (3) 20 g/day soy protein supplement (34 mg/day naturally occurring phytoestrogens) mixed with beverages split into two

equal doses in addition to their usual diets for 6 weeks each (Ref. 172). Blood TC and LDL cholesterol were significantly (P <0.05) lower in the soy protein groups compared to the control group.

Gooderham et al. (1996) was a 28-day randomized, controlled, parallel trial of moderate quality in which 20 Canadian men consumed daily a supplement containing 60 g/day of soy protein isolate (n=10) or a supplement containing 60 g/day of casein (control) (n=10) in addition to their usual diet (Ref. 173). There was no significant difference in blood TC and LDL cholesterol between the soy protein isolate group and casein group.

b. Studies in subjects with desirable or borderline cholesterol levels that were feeding studies or substitution studies with isolated soy protein.

Mangano et al. (2013) was a 1-year, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 97 postmenopausal American women consumed: (1) 18 g/day isolated soy protein plus 105 mg/day isoflavone tablets (n=25); (2) 18 g/day isolated soy protein plus placebo tablets (n=24); (3) 18 g/day control protein (casein, whey, and egg protein) plus 105 mg/day isoflavone tablets (n=26); or (4) control protein and placebo tablets (n=22) in a beverage or food. Subjects were counseled to reduce animal protein foods by approximately 3 oz/day, which is an amount equivalent to the protein powder provided in the study (Ref. 174). There was no significant difference in blood TC or LDL cholesterol between any of the soy protein groups and the control groups.

Steinberg et al. (2003) was a randomized, double-blind, controlled, crossover trial of moderate quality in which 28 postmenopausal American women consumed: (1) 25 g/day of isolated soy protein (107 mg/day naturally occurring isoflavones); (2) 25 g/day of isolated soy protein depleted of isoflavones (2 mg/day isoflavones); and (3) 25 g/day total milk protein (control) for a duration of 6 weeks each (Ref. 175). Subjects mixed the protein powders with a beverage and were instructed to incorporate the protein into their diet without increasing protein or energy intake. There was no significant difference in blood TC and LDL cholesterol between soy protein groups and milk protein control group.

Bakhit et al. (1994) was a randomized, controlled, crossover trial of moderate quality in which 21 American men consumed muffins containing: (1) 25 g/day isolated soy protein plus 20 g/day of dietary fiber from cellulose; (2) 25 g/day isolated soy protein plus 20 g/day of soybean cotyledon fiber; (3) 25 g/day casein plus 20 g/day soybean cotyledon fiber (control); and (4) 25 g/day casein plus 20 g/day of dietary fiber from cellulose (control) for a duration of 4 weeks each (Ref. 176). Subjects were counseled to incorporate the muffins into a low-fat, low-cholesterol diet. There were no significant differences between isolated soy protein groups and control groups for blood TC and LDL cholesterol.

van Raaji et al. (1981) was a 4-week, controlled, parallel trial of moderate quality in which 69 Dutch men and women were fed an average Western diet with different types of dietary protein incorporated into specifically developed products. The dietary protein groups were: (1) 54 g/day of isolated soy protein (n=24); (2) 17 g/day soy (approximately a 2:1 mixture of casein:soy) (n=20); or (3) 55 g/day casein (control) (n=25) (Ref. 177). Participants were matched for initial serum cholesterol, energy intake, and sex. There was no significant difference in blood TC between the isolated soy protein groups and casein control group. However, blood LDL was significantly lower (P <0.05) in the isolated soy protein group compared to the casein control group.

c. Studies in subjects with desirable or borderline cholesterol levels that added soy foods to the diet.

Takatsuka et al. (2000) was a 60-day, randomized, controlled, parallel trial of moderate quality in which 52 premenopausal Japanese women consumed approximately 16 g/day of soy protein from soy milk (n=27) in addition to their usual diet or followed their usual diet as a control diet (n=25) (Ref. 178). The control diet was a usual diet and therefore not a true placebo. The change in blood TC was significantly lower (P = 0.022) in the soy milk group compared to the control group. However, there was no significant difference in the change in blood LDL cholesterol between the two groups.

Mitchell and Collins (1999) was a 4-week, randomized, controlled, parallel trial of moderate quality in which 10 British men consumed: (1) One liter of soy milk (n=4); (2) one liter of rice milk (control) (n=3); or (3) one liter of semi skimmed cow's milk (control) (n=3) in addition to their usual diets. There was no significant difference in blood TC between groups (Ref. 179).

Murkies et al., (1995) was a 12-week randomized, double-blind, controlled parallel trial of moderate quality in which 47 postmenopausal Australian women consumed 45 g/day of wheat flour with an estimated 4.6 g/day wheat protein (control) (n=24) or 45 g/day soy flour with an estimated 15 g/day of soy protein (n=23) in addition to their usual diet (Ref. 180). There was no significant difference in blood TC between the two groups.

d. Studies in subjects with desirable or borderline cholesterol levels that were feeding studies or substitution studies with soy foods.

Matthan et al. (2007) was a randomized, controlled, crossover trial of moderate quality in which 28 American subjects were fed four diets: (1) Animal protein (control), (2) soybean diet (~37.5 g/day soy protein), (3) soy flour (~37.5 g/day soy protein), and (4) and soy milk (~37.5 g/day soy protein) for a duration of 6 weeks each (Ref. 181). Blood LDL cholesterol was significantly lower (P <0.05) in the soymilk diet period compared to the animal protein diet period (control). However, there was no significant difference in blood TC between the soymilk diet period and the animal protein diet period. Furthermore, there was no significant difference in blood TC or LDL cholesterol between the animal protein diet period (control) and the soybean diet period or the soy flour diet period.

Jenkins et al. (1989) was a controlled, crossover trial of moderate quality in which 11 obese Canadian women who consumed a low calorie diet (1,000 kcal) had 2 meals replaced by soy-based liquid formula made from soy flour and soy protein isolate, and a milk-based liquid formula for a duration of 4 weeks each. The soy formula provided approximately 17 g/day soy protein, and the cow's milk formula provided 18 g/day milk protein (control) (Ref. 182). There was no significant difference in blood TC and LDL cholesterol between the soy formula and the cow's milk formula groups.

Bosello et al. (1988) was a 75-day, controlled, parallel trial of moderate quality in which 24 obese Italian subjects were fed a very low calorie diet (375 kcal/day) for 15 days (Ref. 183). The very low calorie diets were then integrated with a commercial textured preparation that provided approximately 27 g/day of casein (control) or approximately 28 g/day soy protein that was consumed daily for 60 days. The 60-day hypocaloric diet provided a total of 800 kcal/day (375 kcal/day from the very low calorie diet and 425 kcal/day from commercial textured preparation). Blood TC and LDL cholesterol was significantly lower (P <0.01) after consuming the soy protein diet compared to the casein diet.

e. Studies that include subjects with normal, borderline, and high cholesterol that were fed or substituted isolated soy protein in the diet.

Greany et al. (2004) was a randomized, controlled, crossover trial of moderate quality in which 33 postmenopausal American women consumed: (1) 26 g/day of soy protein isolate; (2) 26 g/day soy protein isolate plus probiotic capsules; (3) 26 g/day milk protein; and (4) 26 g/day milk protein plus probiotic capsules for a duration of 6 weeks each (Ref. 184). Subjects were counseled to substitute the protein powders in two divided doses for other protein containing foods in their diet. For the analysis, the soy protein and milk protein diets (control), with or without probiotics, were combined. Blood TC and LDL cholesterol was significantly lower ($P < 0.05$) after consuming the soy protein isolate compared to the milk protein control period.

Wong et al. (1998) was a randomized, controlled, crossover trial of high quality in which 13 American subjects with normal or borderline high cholesterol and 13 American subjects with high cholesterol consumed a National Cholesterol Education Program (NCEP) Step 1 soy protein diet that provided approximately 50 g/day isolated soy protein or an NCEP Step 1 animal protein diet that provided approximately 50 g/day animal protein (control) for a duration of 5 weeks each (Ref. 185). Blood LDL cholesterol was significantly lower ($P < 0.05$) after the soy protein period compared to the animal protein period for both the normal and borderline high subjects and high cholesterol subjects. However, there was no significant difference in blood TC between the soy protein diet and the control diet for both the normal and borderline high subjects and high cholesterol subjects.

Goldberg et al. (1982) was a randomized, controlled, crossover trial of moderate quality in which 12 American subjects with high cholesterol and 4 American subjects with normal or borderline high cholesterol consumed daily: (1) An animal protein diet (control); and (2) an isolated soy protein diet for a duration of 6 weeks each. The soy protein diet contained an estimated 99 g/day of isolated soy protein (Ref. 186). Blood TC and LDL cholesterol in the 12 subjects with high cholesterol was significantly lower ($P < 0.025$) after the soy protein diet compared to the animal protein diet. However, there was no significant difference in blood TC and LDL between the two diets in the four subjects with normal or borderline high cholesterol.

f. Studies in subjects with high cholesterol levels that added isolated soy protein to the diet.

Hoie et al. (2007) was an 8-week, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 88 German subjects consumed: (1) 25 g/day of isolated soy protein in its native, non-denatured form (n=28); (2) 25 g/day of isolated soy protein (n=32); or (3) 25 g/day of milk protein (derived from caseinate and skimmed milk powder) (n=28) (control) in addition to their usual diets (Ref. 187). Blood TC and LDL cholesterol was significantly lower ($P < 0.001$ and $P = 0.002$, respectively) after consuming the non-denatured isolated soy protein compared to milk protein group. Blood TC cholesterol was also significantly lower ($P = 0.008$) after consuming isolated soy protein compared to milk protein group. However, there was no significant difference for blood LDL cholesterol after consuming isolated soy protein compared to milk protein group.

Hoie et al. (2006) was a 4-week, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 80 German subjects consumed daily: (1) Ultra-heat-treated chocolate-flavored milk containing 24.4 g/day isolated soy protein and 30.4 g/day milk protein (n=20); (2) 43.3 g/day milk protein (control) (n=20); (3) ultra-heat-treated chocolate flavored milk containing 12.2 g/day isolated soy protein and 15.2 g/day milk protein (n=20); or (4) 21.7 g/day milk protein (control) (n=20) (Ref. 188). There was no significant difference in blood TC or LDL cholesterol between the group that consumed the ultra-heat-treated chocolate-flavored milk containing 24.4 g/day isolated soy protein and 30.4 g/day milk protein group and the control milk protein group. There was also no significant difference in blood TC and LDL cholesterol between the group that consumed ultra-heat-treated chocolate-flavored milk containing 12.2 g/day soy protein and 15.2 g/day milk protein per day (n=20) or the control milk protein group.

Hoie et al. (2005a) was an 8-week, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 77 German subjects consumed 25 g/day soy protein (n=39) or 25 g/day milk protein (derived from caseinate and skimmed milk powder) (control) (n=38) in addition to their usual diets (Ref. 189). Blood LDL cholesterol was significantly lower ($P < 0.05$) in the soy protein group when compared to the casein group. There was no difference in blood TC between the soy protein group and casein group.

Hoie et al. (2005b) was an 8-week, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 117 German subjects consumed: (1) 25 g/day soy protein (n=39); (2) 15 g/day soy protein plus 10 g/day milk protein (derived from caseinate and skimmed milk powder) (n=39); or (3) 25 g/day milk protein (derived from caseinate and skimmed milk powder) (control) (n=39) in addition to their usual diets (Ref. 190). Blood LDL cholesterol was significantly lower ($P = 0.002$) after consumption of 25 g/day soy protein compared to the 25 g/day casein group. TC was also significantly lower ($P = 0.002$) after consumption of 25 g/day soy protein compared to the 25 g/day casein group. In the 15 g/day soy protein plus 10 g/day casein group blood LDL cholesterol was significantly lower ($P = 0.011$) compared to 25 g/day casein control group. TC was also significantly lower ($P = 0.001$) after consumption of 15 g/day soy protein plus 10 g/day casein compared to 25 g/day casein control group.

Teede et al. (2005) was a 3-month, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 40 postmenopausal Australian women consumed 40 g/day isolated soy protein (n=19) or a casein placebo in addition to their usual diet (n=21) (Ref. 191). There was no significant difference in blood TC or LDL cholesterol between the soy protein and casein group.

Harrison et al. (2004) was a 5-week, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 112 British men and women consumed foods (bread, cracker biscuits, and snack bars) that provided 25 g/day isolated soy protein (n=59) or the same foods without soy protein as a control (n=53) in addition to their usual diet (Ref. 192). There was no significant difference in blood TC and LDL cholesterol between the soy protein and control groups.

Blum et al. (2003) was a randomized, double-blind, placebo-controlled, crossover trial of moderate quality in which 24 postmenopausal Israeli women consumed 25 g/day milk protein (control) and 25 g/day isolated soy protein in addition to their usual diets for a duration of 6 weeks each (Ref. 193). Blood TC and LDL cholesterol was significantly lower ($P < 0.05$) after consuming soy protein isolate compared to milk protein period.

Cuevas et al. (2003) was a randomized, double-blind, controlled, crossover trial of moderate quality in which 18 postmenopausal Chilean women consumed diets providing 40 g/

day caseinate (control) and 40 g/day isolated soy protein in addition to an NCEP Step 1 diet for a duration of 4 weeks each (Ref. 194). There was no significant difference in blood TC and LDL cholesterol between the caseinate control diet and soy protein diet.

Gardner et al. (2001) was a 12-week, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 94 postmenopausal American women consumed: (1) 42 g/day total milk protein (control) (n=30); (2) 42 g/day isolated soy protein with isoflavones depleted (3 mg/day) (n=33); or (3) 42 g/day isolated soy protein (80 mg/day naturally occurring isoflavones) (n=31) in addition to their usual diet (Ref. 195). There was no significant difference in blood TC or LDL cholesterol between the isolated soy protein groups and the total milk protein control group.

Hori et al. (2001) was a 3-month, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 21 Taiwanese men consumed: (1) Casein hydrolysate (n=7); (2) 3 g/day of a crude type of soy protein hydrolysate (n=7); or (3) 6 g/day of a crude type of soy protein hydrolysate (n=7) in addition to their usual diet. Blood TC was significantly lower (P <0.05) after consuming 3 g/day of a crude type of soy protein hydrolysate group for 3 months compared to the casein hydrolysate control (Ref. 196). Blood TC was also significantly lower after consuming 6 g/day crude type of soy protein hydrolysate group after 2 and 3 months compared to the casein hydrolysate control. Blood LDL cholesterol was significantly lower (P <0.05) after consuming 3 g/day of a crude type of soy protein hydrolysate group after 2 and 3 months compared to the casein hydrolysate control. Blood LDL cholesterol was also significantly lower (P <0.05) after consuming 6 g/day a crude type of soy protein hydrolysate group after 1, 2, and 3 months compared to the casein hydrolysate group.

g. Studies in subjects with high cholesterol levels that were feeding or substitution studies with isolated soy protein.

Chen et al. (2006) was a 12-week, randomized, double-blind, placebo-controlled, parallel trial of high quality in which 26 Taiwanese subjects on dialysis consumed daily their usual dialysis diet that incorporated 30 g/day milk protein (control) (n=13) or an isolated soy protein diet containing 30 g/day soy protein (n=13) (Ref. 197). Blood TC was significantly lower (P <0.05) in the isolated soy protein diet compared to the milk protein control. There was no significant difference in blood LDL cholesterol between the milk protein control and isolated soy protein diet.

Ma et al. (2005) was a 5-week, randomized, double-blind, controlled, parallel trial of moderate quality in which 159 American subjects consumed daily 28 g/day milk protein supplement (n=78) (control) or a 32 g/day isolated soy protein supplement (n=81) in a beverage. Subjects were counseled to modify their protein and carbohydrate intake to account for the protein supplement intake. There was no significant difference in blood TC and LDL cholesterol between the two diets (Ref. 198).

West et al. (2005) and Hilpert et al. (2005) both discuss a randomized, double-blind, controlled, crossover trial of high quality in which 32 American subjects were fed an NCEP Step 1 diet that incorporated 25 g/day milk protein or 25 g/day soy protein isolate for a duration of 6 weeks each (Ref. 199–200). On each diet, 15 g of the protein supplement was consumed in a muffin while the remaining protein supplement was provided to the subjects to integrate into the meals provided. There was no significant difference in blood TC and LDL cholesterol between the milk protein and soy protein isolate diets.

Jenkins et al. (2002 a and b) was a randomized, single-blind, controlled, crossover trial of moderate quality in which 41 Canadian men and women were fed an NCEP Step 2 diet in which the main protein containing foods were replaced with test foods made with: (1) Approximately 60 g/day dairy and egg protein; (2) 50 g/day of soy protein isolate (10 mg/day naturally occurring isoflavones); and (3) 50 g/day soy protein isolate (73 mg/day naturally occurring isoflavones) for a duration of 1 month each (Ref. 201–202). The percent change in blood TC and LDL cholesterol was significantly lower (P <0.01) after consuming the soy protein diets compared to the dairy and egg protein diet (control).

Lichtenstein et al. (2002) was a randomized, double-blind, controlled, crossover, feeding trial of moderate quality in which 42 American men and women consumed diets of: (1) Isolated soy protein depleted of isoflavones (25 g soy protein/1,000 kcal); (2) isolated soy protein enriched with isoflavones (25 g soy protein plus 50 mg isoflavones/1,000 kcal); (3) animal protein with no added isoflavones (25 g animal protein/1,000 kcal); and (4) animal protein with added isoflavones (25 g animal protein and 50 mg isoflavones/1,000 kcal) for a duration of 6 weeks each (Ref. 203). The mean soy intake for women was 55 g/day and 71 g/day for men. The treatment effects for blood TC and LDL cholesterol were significantly lower (P = 0.017 and P = 0.042, respectively) after consuming the soy protein diets compared to the animal protein diets. For 20 subjects with LCL–C >160 mg/dL, the treatment effects for blood TC and LDL–C were significantly lower (P <0.001 and P = 0.003) after consuming the soy protein diets compared to the animal protein diets. These data were also reported in Wang et al., (2004) and Desroches et al., (2004) (Ref. 204–205).

Van Horn et al. (2001) was a 6-week, randomized, controlled, parallel trial of high quality in which 126 postmenopausal American women consumed an NCEP Step 1 diet in which they isocalorically substituted: (1) Oats and 29 g/day milk protein (n=31) (control); (2) wheat and 29 g/day isolated soy protein (n=31); (3) oats and 29 g/day isolated soy protein (n=31); or (4) wheat and 29 g/day milk protein (n=32) (control) for other carbohydrates and dairy type foods (Ref. 206). There was no significant difference in blood TC or LDL cholesterol between the two control and the two soy protein diets.

h. Studies in subjects with high cholesterol that added soy foods to the diet.

Gardner et al. (2007) was a 4-week, randomized, single-blind, controlled, crossover trial of high quality in which 28 American men and women consumed daily: (1) 1 percent cow's milk (control); (2) whole bean soy milk; and (3) soy protein isolate milk, in addition to an American Heart Association diet (Ref. 207). The whole bean soy milk and the soy protein isolate milk provided 25 g/day of soy protein, and the 1 percent cow's milk provided 25 g/day of milk protein. Blood LDL cholesterol was a significantly lower (P = 0.02) after consuming whole bean soy milk when compared to 1 percent cow's milk. Blood LDL cholesterol was also significantly lower (P = 0.02) after consuming the soy protein diet compared to the 1 percent cow's milk diet.

i. Study in subjects with high cholesterol that were fed soy foods.

Jenkins et al. (2000) was a randomized, controlled, crossover trial of moderate quality in which 25 Canadian men and women consumed daily an NCEP Step 2 diet that incorporated: (1) A commercial breakfast cereal containing 8 g/day wheat protein (control); and (2) a breakfast cereal made with 70 percent soy flour that provided 36 g/day soy protein for a duration of 3 weeks each (Ref. 208). There was no significant

difference between the wheat protein cereal (control) period and soy flour cereal diet period for blood TC and LDL cholesterol.

2. Intervention Studies That Examined Soy Protein Intake and Systolic Blood Pressure (SBP) or Diastolic Blood Pressure (DBP)

Twenty-eight studies, described in 30 publications, either substituted soy protein in the diet or were feeding studies. These studies did not control for or provide information on sodium and potassium intake in the diet (Ref. 44, 55, 66, 74, 77, 84, 91, 96–97, 99, 114, 116, 123, 125–126, 131–132, 139–140, 144, 149–151, 153–154, 181, 201–202, 208–209). Because sodium and potassium intake also influence blood pressure, the independent effects of soy protein intake and blood pressure could not be determined. Therefore, we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from these studies.

Four studies did not include an appropriate control protein for a comparison of the relative effects of soy protein (Ref. 40, 42, 210–211). Without an appropriate control group, it cannot be determined if the changes in SBP or DBP were due to soy protein intake or uncontrolled, extraneous factors. Therefore, we could not draw scientific conclusions about the relationship between soy protein consumption and risk of CHD from these studies.

Chiechi et al. (2002) was a 6-month, randomized, parallel trial in which 67 subjects with pre-hypertension (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg) consumed their usual diet (n=43) or their usual diet plus a soy food serving each day (*e.g.* soy milk, miso soup, tofu, tempeh, or soy beans) (n=34) (Ref. 142). Subjects in the soy group also exchanged two meals twice a week with two meals from a study menu that was based on traditional Mediterranean recipes and soy or soy products. Approximately 50 percent of subjects in the soy group dropped out of the study compared to 20 percent in the control group. Therefore, the dropout rate in the treatment group makes the results of this study difficult to interpret. A high dropout rate can introduce bias because it changed the number of subjects in the treatment group and may also have changed the group's composition compared to the control group. In addition to a high dropout rate, the study had other quality issues (*e.g.,* information on study blinding was not reported, adequate descriptions were not provided for the composition of the background diets or the amount of soy protein in the diets), the study measured biomarkers (SBP or DBP) instead of clinical outcomes (*e.g.,* incidence of CHD). Therefore, this study is so deficient in methodological quality that it is considered to be of low-quality design (Ref. 1) and, as a result, we could not draw scientific conclusions regarding the relationship between soy protein intake and reduced risk of CHD.

a. Studies in subjects with normal or pre-hypertension (SBP <139 mmHg or DBP <89 mmHg).

Anderson et al. (2007) was a 16-week, randomized, single-blind, controlled, parallel trial of moderate quality in which 35 obese American women with pre-hypertension (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg) were fed daily 3 meal replacement shakes containing approximately 22 g/day of casein (control) (n=18) or 21 g/day isolated soy protein (n=17) each (Ref. 89). There was no significant difference in SBP or DBP between the casein and soy protein diet.

Azadbakht et al. (2007) was a randomized, controlled, crossover trial of moderate quality in which 42 postmenopausal Iranian women with pre-hypertension (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg) consumed daily: (1) A Dietary Approaches to Stop Hypertension (DASH) control diet; (2) a 30 g/day soy protein diet; and (3) a 30 g/day soy nut diet for a duration of 8 weeks each (Ref. 65). The soy protein and soy nut diets were the same as the DASH diet with soy protein and soy nuts being substituted for red meat for the control diet. There was no significant difference in SBP or DBP between the DASH control diet and the soy protein and soy nut diets.

Evans et al. (2007) was a randomized, double-blind, placebo-controlled, crossover trial of moderate quality in which 22 pre-hypertensive (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg), postmenopausal American women consumed: (1) 25 g/day isolated soy protein plus 20 g/day soy lecithin; (2) 25 g/day isolated soy protein plus placebo lecithin; (3) placebo protein (50:50 calcium/sodium caseinate) and 20 g/day soy lecithin; and (4) double placebo (protein placebo and soy lecithin) in addition to their usual diet for a duration of 4 weeks each (Ref. 162). There was no significant difference in SBP or DBP between the soy protein plus placebo lecithin group and the double placebo group (control) or between the soy protein plus soy lecithin group and the placebo protein plus soy lecithin period (control).

Harrison et al. (2004) was a 5-week, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 112 British men and women with pre-hypertension (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg) consumed foods (bread, cracker biscuits, and snack bars) that provided 25 g/day isolated soy protein (n=59) or the same foods without soy protein as a control (n=53) in addition to their usual diet (Ref. 192). There was no significant difference in SBP and DBP between the soy protein and control groups.

Cuevas et al. (2003) was a randomized, double-blind, controlled, crossover trial of moderate quality in which 18 pre-hypertensive (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg) postmenopausal Chilean women consumed diets providing 40 g/day caseinate (control) or 40 g/day isolated soy protein in addition to an NCEP Step 1 diet for a duration of 4 weeks each (Ref. 194). There was no significant difference in SBP or DBP between the soy protein diet and caseinate control diet.

Teede et al. (2001) was a 3-month randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 179 pre-hypertensive (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg) Australian men and postmenopausal women consumed a casein placebo (n=93) or 40 g/day soy protein isolate mixed with a beverage twice a day (n=86) in addition to their usual diet (Ref. 170). SBP was significantly lower ($P < 0.05$) in the soy protein isolate group compared to casein control group. However, there was no significant difference in DBP between the casein control group and soy protein isolate group.

Washburn et al. (1999) was a randomized, double-blind, placebo-controlled, crossover trial of moderate quality in which 42 pre-hypertensive (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg), perimenopausal American women consumed: (1) A complex carbohydrate supplement (20 g/day) mixed with a beverage (control); (2) 20 g/day isolated soy protein supplement mixed with a beverage as a single dose; and (3) 20 g/day soy protein supplement mixed with beverages split into two equal doses in addition to their usual diet for a duration of 6 weeks each (Ref. 172). There was no difference in SBP or DBP between the soy protein supplement mixed with a beverage as a single dose period and the complex carbohydrate control period. However, SBP and DBP were significantly lower ($P < 0.05$) after consuming the 20 g/day soy protein supplement mixed with beverages split into two equal doses compared to the complex carbohydrate supplement.

b. Studies in normotensive or pre-hypertensive (SBP <39 mmHg or DBP <89 mmHg) and hypertensive subjects (SBP ≥140 mmHg or DBP ≥90 mmHg).

He et al. (2005) was a 12-week, randomized, double-blind, parallel trial of moderate quality in which 276 Chinese men and women with pre-hypertension (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg) or hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) consumed cookies containing 40 g/day complex carbohydrates from wheat (n=139) (control) or cookies with 40 g/day isolated soy protein (n=137) (Ref. 212). Subjects were instructed to reduce other food intake to keep total energy intake constant. Most subjects consumed the cookies in place of their usual breakfast or usual lunch. SBP and DBP were significantly (P <0.001) lower for those who consumed the soy protein cookies compared to the wheat cookies (control).

Sagara et al. (2004) was a 5-week randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 50 Scottish men with pre-hypertension (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg) or hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) consumed 20 g/day of isolated soy protein powder in biscuits, cereal bars, and bread rolls (n=25) or biscuits, cereal bars, and bread rolls without added soy protein in addition to their usual diets (n=25) (Ref. 166). There was no significant difference in SBP or DBP between the soy protein and control group.

c. Studies in hypertensive subjects (SBP ≥140 mmHg or DBP ≥90 mmHg).

Webb et al. (2008) was a 5-day, randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 25 hypertensive (SBP ≥140 mmHg or DBP ≥90 mmHg) British men and women with CHD consumed 25.7 g/day soy protein isolate (n=13) or 25.7 g/day milk protein isolate (n=12) in addition to their usual diets (Ref. 60). There was no significant difference in SBP or DBP between the soy protein isolate group and the control milk protein isolate group.

Jayagopal et al. (2002) was a randomized, double-blind, placebo-controlled, crossover trial of moderate quality in which 32 hypertensive (SBP ≥140 mmHg or DBP ≥90 mmHg) postmenopausal British women with type 2 diabetes consumed 30 g/day of isolated soy protein or 30 g/day of cellulose (control) in addition to their usual diet for a duration of 12 weeks each (Ref. 169). There was no significant difference in SBP and DBP between the control diet and the soy protein diet.

Rivas et al. (2002) was a 3-month randomized, double-blind, placebo-controlled, parallel trial of moderate quality in which 40 hypertensive (SBP ≥140 mmHg or DBP ≥90 mmHg) Spanish men and women consumed daily 1 liter of soy milk (18 g/day soy protein) or 1 liter of cow's milk (15.5 g/day protein) in addition to their usual diet (Ref. 213). SBP and DBP was significantly lower (P <0.0001) in the soy milk group compared to the cow's milk group.

D. Assessment of Observational Studies

FDA identified 11 observational studies that evaluated soy protein and CHD risk (Ref. 214–224). All of these observational studies calculated soy protein intake from estimated dietary intake. In observational studies that calculated nutrient intake from conventional foods, measures of soy protein intake were based on recorded dietary intake methods such as food frequency questionnaires, diet recalls, or diet records, in which the type and amount of foods consumed were estimated. A common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied as a result of poor memory, over- or underestimation of portion sizes, and recall bias (Ref. 225). Furthermore, the nutrient content of foods can vary due to a number of factors, including soil composition, food processing and cooking procedures, and storage conditions (*e.g.,* duration, temperature). Thus, we cannot ascertain an accurate amount of soy protein consumed based merely on subjects' reports of dietary intake of foods.

In addition, soy foods contain not only soy protein, but also other nutrients that may be associated with the metabolism of soy protein or the pathogenesis of CHD. Therefore, because soy protein containing foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Ref. 3). For studies based on recorded dietary intake of such foods, it is not possible to accurately determine whether any observed effects of soy protein on coronary heart disease risk were due to: (1) Soy protein alone; (2) interactions between soy protein and other nutrients; (3) other nutrients acting alone or together; or (4) decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of soy protein containing foods. In some instances, epidemiological studies based on the recorded dietary intake of conventional foods may indicate a benefit for a particular nutrient with respect to a disease; however, it is subsequently demonstrated in an intervention study that the nutrient-containing dietary supplement does not confer a benefit or actually increases risk of the disease (Ref. 226). For example, previous epidemiological studies reported an association between fruits and vegetables high in beta-carotene and a reduced risk of lung cancer (Ref. 227). However, subsequent intervention studies, the Alpha-Tocopherol and Beta Carotene Prevention Study (ATBC) and the Carotene and Retinol Efficiency Trial (CARET), demonstrated that beta-carotene supplements increase the risk of lung cancer in smokers and asbestos-exposed workers, respectively (Ref. 228–229). These studies illustrate that the effect of a nutrient provided as a dietary supplement exhibits different health effects compared to when it is consumed as part of a usual diet among many other food components. Furthermore, these studies demonstrate the potential public health risk of relying on results from epidemiological studies in which the effect of a nutrient is based on recorded dietary intake of conventional foods as the sole source for concluding that a relationship exists between a specific nutrient and disease risk (*i.e.,* the effect could actually be harmful).

For the reasons provided in this section, scientific conclusions cannot be drawn from observational studies on foods for soy protein as a food ingredient or component of food.

VI. Strength of the Scientific Evidence

In evaluating the scientific evidence using our evidence-based review system (Ref. 1), we considered the strength of evidence for a relationship between soy protein intake and reduced risk of CHD. When evaluating the strength of the evidence, we consider study types, methodological quality, quantity of evidence for and against the claim (taking into account the numbers of various types of studies and study sample sizes), relevance to the U.S. population or target subgroup, replication of study results supporting the claim, and overall consistency of the evidence (beneficial effect, no effect) (Ref. 1). For the outcome of an intervention study to demonstrate an effect, the validated surrogate or clinical endpoint evaluated in the intervention group should be statistically significantly different from the same validated surrogate or clinical endpoint evaluated in the control group (P <0.05). After assessing the totality of the scientific evidence, we then determine whether there is SSA to support an

authorized health claim, or credible evidence to support a qualified health claim.

Our decision about whether to authorize a health claim represents our determination as to whether there is significant scientific agreement among qualified experts that the publicly available scientific evidence supports the substance/disease relationship that is the subject of a proposed health claim. The SSA standard is intended to be a strong standard that provides a high level of confidence in the validity of the substance/disease relationship. SSA occurs well after the stage of emerging science, where data and information permit an inference, but does not require consensus based on unanimous and incontrovertible scientific opinion. We explained in our 2009 guidance (Ref. 1) that we may evaluate new information that becomes available to determine whether it necessitates a change to an existing SSA claim to maximize the public health benefit of our health claims review. The 2009 guidance represents our current thinking on the meaning of the SSA standard in section 403(r)(3) of the FD&C Act and § 101.14(c) and the process for evaluating the scientific evidence for a health claim pursuant to these authorities.

As noted in section V, we reevaluated, consistent with the 2009 guidance (Ref. 1), the studies included in the 1999 final rule as well as new studies that were published since the original review. As discussed in section V.C and D, the totality of the scientific evidence includes 58 well-designed, well-executed intervention studies. Of these 58 studies, 46 are intervention studies of high or moderate quality that measured blood TC or LDL cholesterol, and 12 are intervention studies of high or moderate quality that measured SBP or DBP. The results of these studies were inconsistent and not conclusive.

Of the 46 studies intervention studies of high or moderate quality that measured blood TC or LDL cholesterol, 25 studies were conducted on subjects with desirable or borderline cholesterol levels, defined as a blood TC less than 240 mg/dL or LDL cholesterol less than 160 mg/dL; 18 were conducted on subjects with high TC levels, defined as TC levels less than 240 mg/dL or LDL cholesterol greater than or equal to 160 mg/dL; and 3 studies included subjects with desirable or borderline TC levels and subjects with high TC levels. Of the 46 intervention studies that looked at the relationship between blood TC and/or LCL cholesterol and soy protein intake, only 19 intervention studies showed a benefit in significantly reducing the risk of CHD, while the other 27 intervention studies did not. Study findings also were inconsistent regardless of whether soy protein was added to diet as a supplement or whether the studies were substitution or feeding studies. The study findings also were inconsistent regardless of the study size (10 subjects to 179 subjects) or the dose of soy protein (3 g to 92 g/day). Of the 12 high or moderate quality intervention studies that measured SBP or DBP from which a conclusion could be drawn, only 4 showed a benefit in lowering SBP or DBP with soy protein consumption, while the other 8 studies did not show a benefit. Again, the study findings were inconsistent regardless of baseline SBP or DBP, study size (18 subjects to 276 subjects), or dose (18 g to 60 g/day). Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Ref. 1). The totality of the evidence does not provide a basis on which experts would find SSA because of the high degree of inconsistency of findings across similar and different studies with high or moderate methodological quality. This degree of inconsistency would not be seen when SSA exists because, when there is SSA, we would find most of the studies to consistently find a beneficial relationship between a substance and a disease risk.

Although there is some evidence that suggests a relationship between soy protein intake and reduced risk of CHD, the strength of the totality of the current, publicly available scientific evidence, discussed in sections V and VI and the references cited therein, which includes many studies that post-date the publication of our 1999 rule, is inconsistent and not conclusive. See also tables 4–8 in Ref. 230. The additional evidence now available to us includes a number of new studies that do not support the relationship, and a number of studies that are inconclusive that also do not support a relationship. This combined body of evidence represents the totality of the scientific evidence that is currently available. We have now evaluated this entire body of evidence, which consists of the studies in the 1999 rule as well as new evidence published since that time, using the evidence based process described in our 2009 guidance. The totality of the evidence, which includes the new, non-supportive studies, does not support the statutory standard for authorizing a health claim. We have determined that the totality of the scientific evidence does not provide significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported. Therefore, we have tentatively concluded that, currently, there is not significant scientific agreement among experts, under section 403(r)(3)(B)(i) of the FD&C Act, that a health claim about a relationship between soy protein intake and CHD risk is supported by the evidence. We request comment and any supporting data and information concerning this tentative conclusion. However, while the totality of the publicly available scientific evidence does not support a finding of SSA, if, when we finalize this rule, we conclude there is not SSA, but there is some credible evidence for the use of a qualified health claim about the relationship between soy protein and a reduced risk of CHD, we intend to issue a statement of enforcement discretion for the use of a qualified health claim.

In the 1999 soy protein final rule authorizing the use of a health claim regarding soy protein and the risk of CHD (64 FR 57700) (now codified at § 101.82) (the 1999 authorized soy protein health claim), the petitioner determined that use of soy as a dietary protein is generally recognized as safe. Under the health claim petition process, we evaluate whether the proponent of the claim demonstrates, to FDA's satisfaction, that the food ingredient is ''safe and lawful'' under the applicable food safety provisions of the FD&C Act. In the 1999 soy protein final rule, we concluded that there was not sufficient evidence to challenge the petitioner's assertion that soy protein ingredients are GRAS. The petitioner met the showing required by § 101.14(b)(3)(ii) that the substance be ''safe and lawful.'' We have reviewed the scientific evidence relative to the safety of soy protein as a food ingredient and the evidence does not change our previous conclusion that the use of soy protein at the levels necessary to justify a claim has been demonstrated, to our satisfaction, to be safe and lawful under the applicable food safety provisions of the FD&C Act.

VII. Proposal To Revoke § 101.82

As discussed above, FDA may reevaluate the science related to an authorized health claim and may take action to revoke the claim (see section 403(r)(7)(B) of the FD&C Act (21 U.S.C. 343(r)(7)(B)). Based on our review of the totality of the publicly available scientific evidence, we have tentatively concluded that the SSA standard is not met for a relationship between soy protein and reduced risk of CHD. Therefore, we are proposing to revoke

the soy protein and reduced risk of CHD health claim in § 101.82.

VIII. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct 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). Executive Order 13771 requires that the costs associated with new regulations shall ''be offset by the elimination of existing costs associated with at least two prior regulations.'' It has been determined that this proposed rule is an action that does not impose more than de minimis costs as described below and thus is not a regulatory or deregulatory action for purposes of Executive Order 13771. This proposed rule is a significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because up to 40 small businesses could be required to relabel one or more products, we find that the proposed rule may have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $148 million, using the most current (2016) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in any year expenditure that meets or exceeds this amount.

The costs of this rule are relabeling the estimated 200 to 300 products currently making the health claim. We estimate total annualized costs of $35,000 to $81,000, when the relabeling costs are annualized over 20 years at a 7-percent discount rate. The initial, one-time costs are $370,000 to $860,000.

The benefit of this rule is better information for the consumers who are considering purchasing products with soy protein. This may generate an unknown amount of increased consumer surplus. Some consumers may react to this new information by switching their consumption to products that they enjoy more, or products that still have an authorized health claim. We request public comment on how many consumers are likely to react to the changes in health claims caused by this proposed rule, and what the nature of their reaction will be. By basing their consumption decisions on more recent and accurate scientific information, they will get more consumer surplus, in the form of enjoyment and/or potential health benefits, from the bundle of products they consume.

TABLE 3—COST AND BENEFIT OVERVIEW, USD, ANNUALIZED OVER 20 YEARS

	Low estimate	Mean	High estimate
Costs, 7 percent discount rate	$35,000	$55,000	$81,000
Costs, 3 percent discount rate	25,000	39,000	58,000
Benefits	Consumer Health Benefits and/or Enjoyment		

The Economic Analysis of Impacts of the proposed rule performed in accordance with Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act is available at *https://www.regulations.gov* under the docket number for this proposed rule and at: *https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.*

IX. Proposed Effective Date

We intend that the effective date for a final rule resulting from this rulemaking be 30 days after the final rule's date of publication in the **Federal Register**.

With respect to a compliance date, we intend that any adjustments to a product's labeling occur in a manner consistent with our uniform compliance date (see 81 FR 85156, November 25, 2016). Thus, if we issue a final rule before December 31, 2018, then the compliance date would be January 1, 2020.

X. Analysis of Environmental Impact

We have determined under 21 CFR 25.32(p) that this action, revoking a health claim, is categorically excluded from an environmental assessment or an environmental impact statement.

XI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

XII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires Agencies to ''construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State law conflicts with the exercise of Federal authority under the Federal statute.'' Federal law includes an express preemption provision that preempts ''any requirement respecting any claims of the type described in [21 U.S.C. 343(r)(1)] made in the label or labeling of food that is not identical to the requirement of [21 U.S.C. 343(r)] * * *.'' 21 U.S.C. 343–1(a)(5). However, the statutory provision does not preempt any State requirement respecting a statement in the labeling of food that provides for a warning concerning the safety of the food or component of the food (Pub. L. 101–535, section 6, 104 Stat. 2353 (1990)). If this proposed rule is made final, the final rule would revoke the health claim related to soy protein and coronary heart disease in the label or labeling of food under 21 U.S.C. 343(r).

XIII. References

The following references are on display in the Dockets Management Staff (see **ADDRESSES**) and are available

for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

1. U.S. Food and Drug Administration. ''Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims'', January 2009. Retrieved from: *http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/labelingnutrition/ucm073332.htm.*
2. Balk E.C.M., Chew P, Ip S, Raman G, Kupelnick B, Tatsioni A, Sun Y, Wolk B, DeVine D, Lau J. ''Effects of Soy on Health Outcomes. Summary, Evidence Report/Technology Assessment No. 126. (Prepared by the Tufts-New England Medical Center Evidence-Based Practice Center under Contract No. 290–02–0022.)'', AHRQ Publication No. 05–E024–1 July 2005.
3. Sempos C.T., Liu K., Ernst N.D. ''Food and Nutrient Exposures: What to Consider When Evaluating Epidemiologic Evidence''. *American Journal of Clinical Nutrition.* 1999;69:1330S–1338S.
4. Institute of Medicine (IOM) of the National Academies. ''Dietary Supplements: A Framework for Evaluating Safety, Chapter 7, Categories of Scientific Evidence—in Vitro Data.'', Washington, DC; 2005.
5. Spilker B. *Guide to Clinical Studies.* New York, New York: Raven Press, 1991; pp. 59–64, 497–501, 793–800.
6. National Research Council. *Reference Manual on Scientific Evidence: Third Edition.* Washington, DC: The National Academies Press, 2011; pp. 220.
7. Wilson E.B. *An Introduction to Scientific Research.* New York: Dover Publications, 1990; pp. 46–48.
8. Hill A.B. ''The Environment and Disease: Association or Causation?''. *Proceedings of the Royal Society of Medicine.* 1965;58:295–300.
9. Agency for Healthcare Research and Quality. ''Systems to Rate the Scientific Evidence'', March 2002.
10. Institute of Medicine (IOM) of the National Academies. ''Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients), Chapter 8: Dietary Fats: Total Fat and Fatty Acids'', Washington, DC: National Academies Press; 2002.
11. Institute of Medicine (IOM) of the National Academies. ''Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients), Chapter 9: Cholesterol'', Washington, DC: National Academies Press; 2002.
12. Institute of Medicine (IOM) of the National Academies. ''Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients), Chapter 7: Dietary, Functional, and Total Fiber'', Washington, DC: National Academies Press; 2002.
13. U.S. Department of Agriculture. ''Soy Milk'', USDA National Nutrient Database for Standard Reference, release 28, 2016. Retrieved from: *https://ndb.nal.usda.gov/ndb/.*
14. U.S. Department of Agriculture. ''Soy Flour'', USDA National Nutrient Database for Standard Reference, release 28, 2016. Retrieved from: *https://ndb.nal.usda.gov/ndb/.*
15. U.S. Department of Agriculture. ''Soy Protein Isolate'', USDA National Nutrient Database for Standard Reference, release 28, 2016. Retrieved from: *https://ndb.nal.usda.gov/ndb/.*
16. Institute of Medicine (IOM) of the National Academies. ''Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate'', Washington, DC: National Academies Press; 2005.
17. Persky V.W., Turyk M.E., Wang L., Freels S., Chatterton R., Jr., Barnes S., Erdman J., Jr., Sepkovic D.W., Bradlow H.L., Potter S. ''Effect of Soy Protein on Endogenous Hormones in Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2002;75:145–153.
18. Siefker K., DiSilvestro R.A. ''Safety and Antioxidant Effects of a Modest Soy Protein Intervention in Hemodialysis Patients''. *Journal of Medicinal Food.* 2006;9:368–372.
19. Tormala R.M., Nikander E., Tiitinen A., Vaisanen-Tommiska M., Ylikorkala O., Mikkola T.S. ''Serum Cholesterol Efflux Potential in Postmenopausal Women Treated with Isolated Isoflavones''. *Menopause.* 2006;13:96–101.
20. Wiseman H., O'Reilly J.D., Adlercreutz H., Mallet A.I., Bowey E.A., Rowland I.R., Sanders T.A. ''Isoflavone Phytoestrogens Consumed in Soy Decrease F(2)-Isoprostane Concentrations and Increase Resistance of Low-Density Lipoprotein to Oxidation in Humans''. *American Journal of Clinical Nutrition.* 2000;72:395–400.
21. Hill S., Box W., DiSilvestro R.A. ''Moderate Intensity Resistance Exercise, Plus or Minus Soy Intake: Effects on Serum Lipid Peroxides in Young Adult Males''. *International Journal of Sport Nutrition and Exercise Metabolism.* 2004;14:125–132.
22. Heneman K.M., Chang H.C., Prior R.L., Steinberg F.M. ''Soy Protein with and without Isoflavones Fails to Substantially Increase Postprandial Antioxidant Capacity''. *Journal of Nutritional Biochemistry.* 2007;18:46–53.
23. Greany K.A., Nettleton J.A., Wangen K.E., Thomas W., Kurzer M.S. ''Consumption of Isoflavone-Rich Soy Protein Does Not Alter Homocysteine or Markers of Inflammation in Postmenopausal Women''. *European Journal of Clinical Nutrition.* 2008;62:1419–1425.
24. Vega-Lopez S., Yeum K.J., Lecker J.L., Ausman L.M., Johnson E.J., Devaraj S., Jialal I., Lichtenstein A.H. ''Plasma Antioxidant Capacity in Response to Diets High in Soy or Animal Protein with or without Isoflavones''. *American Journal of Clinical Nutrition.* 2005;81:43–49.
25. Hanson L.N., Engelman H.M., Alekel D.L., Schalinske K.L., Kohut M.L., Reddy M.B. ''Effects of Soy Isoflavones and Phytate on Homocysteine, C-Reactive Protein, and Iron Status in Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2006;84:774–780.
26. Higashi K., Abata S., Iwamoto N., Ogura M., Yamashita T., Ishikawa O., Ohslzu F., Nakamura H. ''Effects of Soy Protein on Levels of Remnant-Like Particles Cholesterol and Vitamin E in Healthy Men''. *Journal of Nutritional Science and Vitaminology.* 2001;47:283–288.
27. Urban D., Irwin W., Kirk M., Markiewicz M.A., Myers R., Smith M., Weiss H., Grizzle W.E., Barnes S. ''The Effect of Isolated Soy Protein on Plasma Biomarkers in Elderly Men with Elevated Serum Prostate Specific Antigen''. *Journal of Urology.* 2001;165:294–300.
28. Cupisti A., D'Alessandro C., Ghiadoni L., Morelli E., Panichi V., Barsotti G. ''Effect of a Soy Protein Diet on Serum Lipids of Renal Transplant Patients''. *Journal of Renal Nutrition.* 2004;14:31–35.
29. Gallagher J.C., Satpathy R., Rafferty K., Haynatzka V. ''The Effect of Soy Protein Isolate on Bone Metabolism''. *Menopause.* 2004;11:290–298.
30. Tonstad S., Smerud K., Hoie L. ''A Comparison of the Effects of 2 Doses of Soy Protein or Casein on Serum Lipids, Serum Lipoproteins, and Plasma Total Homocysteine in Hypercholesterolemic Subjects''. *American Journal of Clinical Nutrition.* 2002;76:78–84.
31. Wangen K.E., Duncan A.M., Xu X., Kurzer M.S. ''Soy Isoflavones Improve Plasma Lipids in Normocholesterolemic and Mildly Hypercholesterolemic Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2001;73:225–231.
32. Yildirir A., Tokgozoglu S.L., Oduncu T., Oto A., Haznedaroglu I., Akinci D., Koksal G., Sade E., Kirazli S., Kes S. ''Soy Protein Diet Significantly Improves Endothelial Function and Lipid Parameters''. *Clinical Cardiology.* 2001;24:711–716.
33. Merz-Demlow B.E., Duncan A.M., Wangen K.E., Xu X., Carr T.P., Phipps W.R., Kurzer M.S. ''Soy Isoflavones Improve Plasma Lipids in Normocholesterolemic, Premenopausal Women''. *American Journal of Clinical Nutrition.* 2000;71:1462–1469.
34. Wong W.W., Hachey D.L., Clarke L.L., Zhang S. ''Cholesterol Synthesis and Absorption by 2h2o and 18o-Cholesterol and Hypocholesterolemic Effect of Soy Protein''. *Journal of Nutrition.* 1995;125:612S–618S.
35. Sathyapalan T., Manuchehri A.M., Thatcher N.J., Rigby A.S., Chapman T., Kilpatrick E.S., Atkin S.L. ''The Effect of Soy Phytoestrogen Supplementation on Thyroid Status and Cardiovascular Risk Markers in Patients with Subclinical Hypothyroidism: A Randomized,

Double-Blind, Crossover Study''. *Journal of Clinical Endocrinology and Metabolism.* 2011;96:1442–1449.
36. Mackey R., Ekangaki A., Eden J.A. ''The Effects of Soy Protein in Women and Men with Elevated Plasma Lipids''. *Biofactors.* 2000;12:251–257.
37. Engelman H.M., Alekel D.L., Hanson L.N., Kanthasamy A.G., Reddy M.B. ''Blood Lipid and Oxidative Stress Responses to Soy Protein with Isoflavones and Phytic Acid in Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2005;81:590–596.
38. Scheiber M.D., Liu J.H., Subbiah M.T., Rebar R.W., Setchell K.D. ''Dietary Inclusion of Whole Soy Foods Results in Significant Reductions in Clinical Risk Factors for Osteoporosis and Cardiovascular Disease in Normal Postmenopausal Women''. *Menopause.* 2001;8:384–392.
39. Ristic Medic D., Ristic V., Arsic A., Postic M., Ristic G., Blazencic Mladenovic V., Tepsic J. ''Effects of Soybean D-Lecivita Product on Serum Lipids and Fatty Acid Composition in Type 2 Diabetic Patients with Hyperlipidemia''. *Nutrition, Metabolism and Cardiovascular Diseases.* 2006;16:395–404.
40. Jenkins D.J., Kendall C.W., Nguyen T.H., Marchie A., Faulkner D.A., Ireland C., Josse A.R., Vidgen E., Trautwein E.A., Lapsley K.G., Holmes C., Josse R.G., Leiter L.A., Connelly P.W., Singer W. ''Effect of Plant Sterols in Combination with Other Cholesterol-Lowering Foods''. *Metabolism.* 2008;57:130–139.
41. Sirtori C.R., Gatti E., Mantero O., Conti F., Agradi E., Tremoli E., Sirtori M., Fraterrigo L., Tavazzi L., Kritchevsky D. ''Clinical Experience with the Soybean Protein Diet in the Treatment of Hypercholesterolemia''. *American Journal of Clinical Nutrition.* 1979;32:1645–1658.
42. Hermansen K., Sondergaard M., Hoie L., Carstensen M., Brock B. ''Beneficial Effects of a Soy-Based Dietary Supplement on Lipid Levels and Cardiovascular Risk Markers in Type 2 Diabetic Subjects''. *Diabetes Care.* 2001;24:228–233.
43. Onning G., Akesson B., Oste R., Lundquist I. ''Effects of Consumption of Oat Milk, Soya Milk, or Cow's Milk on Plasma Lipids and Antioxidative Capacity in Healthy Subjects''. *Annals of Nutrition and Metabolism.* 1998;42:211–220.
44. Cupisti A., Ghiadoni L., D'Alessandro C., Kardasz I., Morelli E., Panichi V., Locati D., Morandi S., Saba A., Barsotti G., Taddei S., Arnoldi A., Salvetti A. ''Soy Protein Diet Improves Endothelial Dysfunction in Renal Transplant Patients''. *Nephrology Dialysis Transplantation.* 2007;22:229–234.
45. Gardner-Thorpe D., O'Hagen C., Young I., Lewis S.J. ''Dietary Supplements of Soya Flour Lower Serum Testosterone Concentrations and Improve Markers of Oxidative Stress in Men''. *European Journal of Clinical Nutrition.* 2003;57:100–106.
46. Lovati M.R., Manzoni C., Canavesi A., Sirtori M., Vaccarino V., Marchi M., Gaddi G., Sirtori C.R. ''Soybean Protein Diet Increases Low Density Lipoprotein Receptor Activity in Mononuclear Cells from Hypercholesterolemic Patients''. *Journal of Clinical Investigation.* 1987;80:1498–1502.
47. Holmes W., Rubel G., Hood S. ''Comparison of the Effect of Dietary Meat Verus Dietary Soybean Protein on Plasma Lipids of Hyperlipidemic Individuals''. *Atherosclerosis.* 1980;36:379–387.
48. Sirtori C.R., Agradi E., Conti F., Mantero O., Gatti E. ''Soybean-Protein Diet in the Treatment of Type-Ii Hyperlipoproteinaemia''. *Lancet.* 1977;1:275–277.
49. Shorey R.L., Bazan B., Lo G.S., Steinke F.H. ''Determinants of Hypocholesterolemic Response to Soy and Animal Protein-Based Diets''. *American Journal of Clinical Nutrition.* 1981;34:1769–1778.
50. Borodin E.A., Menshikova I.G., Dorovskikh V.A., Feoktistova N.A., Shtarberg M.A., Yamamoto T., Takamatsu K., Mori H., Yamamoto S. ''Effects of Two-Month Consumption of 30 G a Day of Soy Protein Isolate or Skimmed Curd Protein on Blood Lipid Concentration in Russian Adults with Hyperlipidemia''. *Journal of Nutritional Science and Vitaminology.* 2009;55:492–497.
51. Potter J.M., Nestel P.J. ''Greater Bile Acid Excretion with Soy Bean Than with Cow Milk in Infants''. *American Journal of Clinical Nutrition.* 1976;29:546–551.
52. Takahashi K., Kamada Y., Hiraoka-Yamamoto J., Mori M., Nagata R., Hashimoto K., Aizawa T., Matsuda K., Kometani T., Ikeda K., Yamori Y. ''Effect of a Soybean Product on Serum Lipid Levels in Female University Students''. *Clinical and Experimental Pharmacology and Physiology.* 2004;31 Suppl 2:S42–43.
53. Campbell C.G., Brown B.D., Dufner D., Thorland W.G. ''Effects of Soy or Milk Protein During a High-Fat Feeding Challenge on Oxidative Stress, Inflammation, and Lipids in Healthy Men''. *Lipids.* 2006;41:257–265.
54. Meredith L., Liebman M., Graves K. ''Alterations in Plasma Lipid Levels Resulting from Tofu and Cheese Consumption in Adult Women''. *Journal of the American College of Nutrition.* 1989;8:573–579.
55. Fujii M., Fukui T., Miyoshi T. ''Effect of Freeze-Dried Soybean Curd (Tofu) on Various Bodily Functions''. *Journal of Medical Investigation.* 1999;46:67–74.
56. Fumagalli R., Soleri L., Farina R., Musanti R., Mantero O., Noseda G., Gatti E., Sirtori C.R. ''Fecal Cholesterol Excretion Studies in Type Ii Hypercholesterolemic Patients Treated with the Soybean Protein Diet''. *Atherosclerosis.* 1982;43:341–353.
57. Vessby B., Karlstrom B., Lithell H., Gustafsson I.B., Werner I. ''The Effects on Lipid and Carbohydrate Metabolism of Replacing Some Animal Protein by Soy-Protein in a Lipid-Lowering Diet for Hypercholesterolaemic Patients''. *Human Nutrition Applied Nutrition.* 1982;36:179–189.
58. Sanders T.A., Dean T.S., Grainger D., Miller G.J., Wiseman H. ''Moderate Intakes of Intact Soy Protein Rich in Isoflavones Compared with Ethanol-Extracted Soy Protein Increase Hdl but Do Not Influence Transforming Growth Factor Beta(1) Concentrations and Hemostatic Risk Factors for Coronary Heart Disease in Healthy Subjects''. *American Journal of Clinical Nutrition.* 2002;76:373–377.
59. Blumenschein S., Torres E., Kushmaul E., Crawford J., Fixler D. ''Effect of Oat Bran/Soy Protein in Hypercholesterolemic Children''. *Annals of the New York Academy of Science.* 1991;623:413–415.
60. Webb C.M., Hayward C.S., Mason M.J., Ilsley C.D., Collins P. ''Coronary Vasomotor and Blood Flow Responses to Isoflavone-Intact Soya Protein in Subjects with Coronary Heart Disease or Risk Factors for Coronary Heart Disease''. *Clinical Science.* 2008;115:353–359.
61. Bonanome A., Grundy S.M. ''Effect of Dietary Stearic Acid on Plasma Cholesterol and Lipoprotein Levels''. *New England Journal of Medicine.* 1988;318:1244–1248.
62. Tabibi H., Imani H., Hedayati M., Atabak S., Rahmani L. ''Effects of Soy Consumption on Serum Lipids and Apoproteins in Peritoneal Dialysis Patients: A Randomized Controlled Trial''. *Peritoneal Dialysis International.* 2010;30:611–618.
63. St-Onge M.P., Claps N., Wolper C., Heymsfield S.B. ''Supplementation with Soy-Protein-Rich Foods Does Not Enhance Weight Loss''. *Journal of the Americian Dietetic Association.* 2007;107:500–505.
64. van Raaij J.M., Katan M.B., West C.E., Hautvast J.G. ''Influence of Diets Containing Casein, Soy Isolate, and Soy Concentrate on Serum Cholesterol and Lipoproteins in Middle-Aged Volunteers''. *American Journal of Clinical Nutrition.* 1982;35:925–934.
65. Azadbakht L., Kimiagar M., Mehrabi Y., Esmaillzadeh A., Padyab M., Hu F.B., Willett W.C. ''Soy Inclusion in the Diet Improves Features of the Metabolic Syndrome: A Randomized Crossover Study in Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2007;85:735–741.
66. Jenkins D.J., Kendall C.W., Mehling C.C., Parker T., Rao A.V., Agarwal S., Novokmet R., Jones P.J., Raeini M., Story J.A., Furumoto E., Vidgen E., Griffin L.C., Cunnane S.C., Ryan M.A., Connelly P.W. ''Combined Effect of Vegetable Protein (Soy) and Soluble Fiber Added to a Standard Cholesterol-Lowering Diet''. *Metabolism.* 1999;48:809–816.
67. Pipe E.A., Gobert C.P., Capes S.E., Darlington G.A., Lampe J.W., Duncan A.M. ''Soy Protein Reduces Serum Ldl Cholesterol and the Ldl Cholesterol:Hdl Cholesterol and Apolipoprotein B:Apolipoprotein a-I Ratios in Adults with Type 2 Diabetes''. *Journal of Nutrition.* 2009;139:1700–1706.

68. Haub M.D., Wells A.M., Campbell W.W. ''Beef and Soy-Based Food Supplements Differentially Affect Serum Lipoprotein-Lipid Profiles Because of Changes in Carbohydrate Intake and Novel Nutrient Intake Ratios in Older Men Who Resistive-Train''. *Metabolism.* 2005;54:769–774.
69. Stephenson T.J., Setchell K.D., Kendall C.W., Jenkins D.J., Anderson J.W., Fanti P. ''Effect of Soy Protein-Rich Diet on Renal Function in Young Adults with Insulin-Dependent Diabetes Mellitus''. *Clinical Nephrology.* 2005;64:1–11.
70. Azadbakht L., Atabak S., Esmaillzadeh A. ''Soy Protein Intake, Cardiorenal Indices, and C-Reactive Protein in Type 2 Diabetes with Nephropathy: A Longitudinal Randomized Clinical Trial''. *Diabetes Care.* 2008;31:648–654.
71. Thorp A.A., Howe P.R., Mori T.A., Coates A.M., Buckley J.D., Hodgson J., Mansour J., Meyer B.J. ''Soy Food Consumption Does Not Lower Ldl Cholesterol in Either Equol or Nonequol Producers''. *American Journal of Clinical Nutrition.* 2008;88:298–304.
72. Allen J.K., Becker D.M., Kwiterovich P.O., Lindenstruth K.A., Curtis C. ''Effect of Soy Protein-Containing Isoflavones on Lipoproteins in Postmenopausal Women''. *Menopause.* 2007;14:106–114.
73. Bricarello L.P., Kasinski N., Bertolami M.C., Faludi A., Pinto L.A., Relvas W.G., Izar M.C., Ihara S.S., Tufik S., Fonseca F.A. ''Comparison between the Effects of Soy Milk and Non-Fat Cow Milk on Lipid Profile and Lipid Peroxidation in Patients with Primary Hypercholesterolemia''. *Nutrition.* 2004;20:200–204.
74. Meyer B.J., Larkin T.A., Owen A.J., Astheimer L.B., Tapsell L.C., Howe P.R. ''Limited Lipid-Lowering Effects of Regular Consumption of Whole Soybean Foods''. *Annals of Nutrition and Metabolism.* 2004;48:67–78.
75. Ridges L., Sunderland R., Moerman K., Meyer B., Astheimer L., Howe P. ''Cholesterol Lowering Benefits of Soy and Linseed Enriched Foods''. *Asia Pacific Journal of Clinical Nutrition.* 2001;10:204–211.
76. Widhalm K., Brazda G., Schneider B., Kohl S. ''Effect of Soy Protein Diet Versus Standard Low Fat, Low Cholesterol Diet on Lipid and Lipoprotein Levels in Children with Familial or Polygenic Hypercholesterolemia''. *Journal of Pediatrics.* 1993;123:30–34.
77. Kurowska E.M., Jordan J., Spence J.D., Wetmore S., Piche L.A., Radzikowski M., Dandona P., Carroll K.K. ''Effects of Substituting Dietary Soybean Protein and Oil for Milk Protein and Fat in Subjects with Hypercholesterolemia''. *Clinical Investigative Medicine.* 1997;20:162–170.
78. Ashton E.L., Dalais F.S., Ball M.J. ''Effect of Meat Replacement by Tofu on Chd Risk Factors Including Copper Induced Ldl Oxidation''. *Journal of the American College of Nutrition.* 2000;19:761–767.
79. Ashton E., Ball M. ''Effects of Soy as Tofu Vs Meat on Lipoprotein Concentrations''. *European Journal of Clinical Nutrition.* 2000;54:14–19.
80. Gaddi A., Ciarrocchi A., Matteucci A., Rimondi S., Ravaglia G., Descovich G.C., Sirtori C.R. ''Dietary Treatment for Familial Hypercholesterolemia—Differential Effects of Dietary Soy Protein According to the Apolipoprotein E Phenotypes''. *American Journal of Clinical Nutrition.* 1991;53:1191–1196.
81. Gaddi A., Descovich G.C., Noseda G., Fragiacomo C., Nicolini A., Montanari G., Vanetti G., Sirtori M., Gatti E., Sirtori C.R. ''Hypercholesterolaemia Treated by Soybean Protein Diet''. *Archives of Diseases in Childhood.* 1987;62:274–278.
82. Duane W.C. ''Effects of Soybean Protein and Very Low Dietary Cholesterol on Serum Lipids, Biliary Lipids, and Fecal Sterols in Humans''. *Metabolism.* 1999;48:489–494.
83. Grundy S.M., Abrams J.J. ''Comparison of Actions of Soy Protein and Casein on Metabolism of Plasma Lipoproteins and Cholesterol in Humans''. *American Journal of Clinical Nutrition.* 1983;38:245–252.
84. Hermansen K., Hansen B., Jacobsen R., Clausen P., Dalgaard M., Dinesen B., Holst J.J., Pedersen E., Astrup A. ''Effects of Soy Supplementation on Blood Lipids and Arterial Function in Hypercholesterolaemic Subjects''. *European Journal of Clinical Nutrition.* 2005;59:843–850.
85. Baum J.A., Teng H., Erdman J.W., Jr., Weigel R.M., Klein B.P., Persky V.W., Freels S., Surya P., Bakhit R.M., Ramos E., Shay N.F., Potter S.M. ''Long-Term Intake of Soy Protein Improves Blood Lipid Profiles and Increases Mononuclear Cell Low-Density-Lipoprotein Receptor Messenger Rna in Hypercholesterolemic, Postmenopausal Women''. *American Journal of Clinical Nutrition.* 1998;68:545–551.
86. Potter S.M., Baum J.A., Teng H., Stillman R.J., Shay N.F., Erdman J.W., Jr. ''Soy Protein and Isoflavones: Their Effects on Blood Lipids and Bone Density in Postmenopausal Women''. *American Journal of Clinical Nutrition.* 1998;68:1375S–1379S.
87. Wang M.F., Yamamoto S., Chung H.M., Chung S.Y., Miyatani S., Mori M., Okita T., Sugano M. ''Antihypercholesterolemic Effect of Undigested Fraction of Soybean Protein in Young Female Volunteers''. *Journal of Nutritional Science and Vitaminology.* 1995;41:187–195.
88. Potter S.M., Bakhit R.M., Essex-Sorlie D.L., Weingartner K.E., Chapman K.M., Nelson R.A., Prabhudesai M., Savage W.D., Nelson A.I., Winter L.W., . ''Depression of Plasma Cholesterol in Men by Consumption of Baked Products Containing Soy Protein''. *American Journal of Clinical Nutrition.* 1993;58:501–506.
89. Anderson J.W., Fuller J., Patterson K., Blair R., Tabor A. ''Soy Compared to Casein Meal Replacement Shakes with Energy-Restricted Diets for Obese Women: Randomized Controlled Trial''. *Metabolism.* 2007;56:280–288.
90. Campbell S.C., Khalil D.A., Payton M.E., Arjmandi B.H. ''One-Year Soy Protein Supplementation Does Not Improve Lipid Profile in Postmenopausal Women''. *Menopause.* 2010;17:587–593.
91. Anderson J.W., Hoie L.H. ''Weight Loss and Lipid Changes with Low-Energy Diets: Comparator Study of Milk-Based Versus Soy-Based Liquid Meal Replacement Interventions''. *Journal of the American College of Nutrition.* 2005;24:210–216.
92. Wu A.H., Stanczyk F.Z., Martinez C., Tseng C.C., Hendrich S., Murphy P., Chaikittisilpa S., Stram D.O., Pike M.C. ''A Controlled 2-Mo Dietary Fat Reduction and Soy Food Supplementation Study in Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2005;81:1133–1141.
93. Steele M.G. ''The Effect on Serum Cholesterol Levels of Substituting Milk with a Soya Beverage''. *Australian Journal of Nutrition and Dietetics.* 1992;49:24–28.
94. Deibert P., Konig D., Schmidt-Trucksaess A., Zaenker K.S., Frey I., Landmann U., Berg A. ''Weight Loss without Losing Muscle Mass in Pre-Obese and Obese Subjects Induced by a High-Soy-Protein Diet''. *International Journal of Obesity.* 2004;28:1349–1352.
95. Puska P., Korpelainen V., Hoie L.H., Skovlund E., Lahti T., Smerud K.T. ''Soy in Hypercholesterolaemia: A Double-Blind, Placebo-Controlled Trial''. *European Journal of Clinical Nutrition.* 2002;56:352–357.
96. Puska P., Korpelainen V., Hoie L.H., Skovlund E., Smerud K.T. ''Isolated Soya Protein with Standardised Levels of Isoflavones, Cotyledon Soya Fibres and Soya Phospholipids Improves Plasma Lipids in Hypercholesterolaemia: A Double-Blind, Placebo-Controlled Trial of a Yoghurt Formulation''. *British Journal of Nutrition.* 2004;91:393–401.
97. Allison D.B., Gadbury G., Schwartz L.G., Murugesan R., Kraker J.L., Heshka S., Fontaine K.R., Heymsfield S.B. ''A Novel Soy-Based Meal Replacement Formula for Weight Loss among Obese Individuals: A Randomized Controlled Clinical Trial''. *European Journal of Clinical Nutrition.* 2003;57:514–522.
98. Kreijkamp-Kaspers S., Kok L., Grobbee D.E., de Haan E.H., Aleman A., Lampe J.W., van der Schouw Y.T. ''Effect of Soy Protein Containing Isoflavones on Cognitive Function, Bone Mineral Density, and Plasma Lipids in Postmenopausal Women: A Randomized Controlled Trial''. *Journal of the American Medical Association.* 2004;292:65–74.
99. Kreijkamp-Kaspers S., Kok L., Bots M.L., Grobbee D.E., Lampe J.W., van der Schouw Y.T. ''Randomized Controlled Trial of the Effects of Soy Protein Containing Isoflavones on Vascular Function in Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2005;81:189–195.
100. Dent S.B., Peterson C.T., Brace L.D., Swain J.H., Reddy M.B., Hanson K.B., Robinson J.G., Alekel D.L. ''Soy Protein Intake by Perimenopausal Women Does

Not Affect Circulating Lipids and Lipoproteins or Coagulation and Fibrinolytic Factors''. *Journal of Nutrition.* 2001;131:2280–2287.
101. Swain J.H., Alekel D.L., Dent S.B., Peterson C.T., Reddy M.B. ''Iron Indexes and Total Antioxidant Status in Response to Soy Protein Intake in Perimenopausal Women''. *American Journal of Clinical Nutrition.* 2002;76:165–171.
102. Sirtori C.R., Bosisio R., Pazzucconi F., Bondioli A., Gatti E., Lovati M.R., Murphy P. ''Soy Milk with a High Glycitein Content Does Not Reduce Low-Density Lipoprotein Cholesterolemia in Type Ii Hypercholesterolemic Patients''. *Annals of Nutrition and Metabolism.* 2002;46:88–92.
103. Sirtori C.R., Zucchi-Dentone C., Sirtori M., Gatti E., Descovich G.C., Gaddi A., Cattin L., Da Col P.G., Senin U., Mannarino E., . ''Cholesterol-Lowering and Hdl-Raising Properties of Lecithinated Soy Proteins in Type Ii Hyperlipidemic Patients''. *Annals of Nutrition and Metabolism.* 1985;29:348–357.
104. Sirtori C.R., Pazzucconi F., Colombo L., Battistin P., Bondioli A., Descheemaeker K. ''Double-Blind Study of the Addition of High-Protein Soya Milk V. Cows' Milk to the Diet of Patients with Severe Hypercholesterolaemia and Resistance to or Intolerance of Statins''. *British Journal of Nutrition.* 1999;82:91–96.
105. Descovich G.C., Ceredi C., Gaddi A., Benassi M.S., Mannino G., Colombo L., Cattin L., Fontana G., Senin U., Mannarino E., Caruzzo C., Bertelli E., Fragiacomo C., Noseda G., Sirtori M., Sirtori C.R. ''Multicentre Study of Soybean Protein Diet for Outpatient Hyper-Cholesterolaemic Patients''. *Lancet.* 1980;2:709–712.
106. Carroll K.K., Giovannetti P.M., Huff M.W., Moase O., Roberts DC, Wolfe B.M. ''Hypocholesterolemic Effect of Substituting Soybean Protein for Animal Protein in the Diet of Healthy Young Women''. *American Journal of Clinical Nutrition.* 1978;31:1312–1321.
107. Giovannetti P.M., Carroll K.K., Wolfe B.M. ''Constancy of Fasting Serum Cholesterol of Healthy Young Women Upon Substitution of Soy Protein Isolate for Meat and Dairy Protein in Medium and Low Fat Diets''. *Nutrition Research.* 1986;6:609–618.
108. Sacks F.M., Breslow J.L., Wood P.G., Kass E.H. ''Lack of an Effect of Dairy Protein (Casein) and Soy Protein on Plasma Cholesterol of Strict Vegetarians. An Experiment and a Critical Review''. *Journal of Lipid Research.* 1983;24:1012–1020.
109. Meinertz H., Nilausen K., Hilden J. ''Alcohol-Extracted, but Not Intact, Dietary Soy Protein Lowers Lipoprotein(a) Markedly''. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2002;22:312–316.
110. Nilausen K., Meinertz H. ''Variable Lipemic Response to Dietary Soy Protein in Healthy, Normolipemic Men''. *American Journal of Clinical Nutrition.* 1998;68:1380S–1384S.
111. Nilausen K., Meinertz H. ''Lipoprotein(a) and Dietary Proteins: Casein Lowers Lipoprotein(a) Concentrations as Compared with Soy Protein''. *American Journal of Clinical Nutrition.* 1999;69:419–425.
112. Meinertz H., Faergeman O., Nilausen K., Chapman M.J., Goldstein S., Laplaud P.M. ''Effects of Soy Protein and Casein in Low Cholesterol Diets on Plasma Lipoproteins in Normolipidemic Subjects''. *Atherosclerosis.* 1988;72:63–70.
113. Meinertz H., Nilausen K., Faergeman O. ''Soy Protein and Casein in Cholesterol-Enriched Diets: Effects on Plasma Lipoproteins in Normolipidemic Subjects''. *American Journal of Clinical Nutrition.* 1989;50:786–793.
114. Welty F.K., Lee K.S., Lew N.S., Zhou J.R. ''Effect of Soy Nuts on Blood Pressure and Lipid Levels in Hypertensive, Prehypertensive, and Normotensive Postmenopausal Women''. *Archives of Internal Medicine.* 2007;167:1060–1067.
115. Teixeira S.R., Potter S.M., Weigel R., Hannum S., Erdman J.W., Jr., Hasler C.M. ''Effects of Feeding 4 Levels of Soy Protein for 3 and 6 Wk on Blood Lipids and Apolipoproteins in Moderately Hypercholesterolemic Men''. *American Journal of Clinical Nutrition.* 2000;71:1077–1084.
116. Crouse J.R., III, Morgan T., Terry J.G., Ellis J., Vitolins M., Burke G.L. ''A Randomized Trial Comparing the Effect of Casein with That of Soy Protein Containing Varying Amounts of Isoflavones on Plasma Concentrations of Lipids and Lipoproteins''. *Arch Intern Med.* 1999;159:2070–2076.
117. Weghuber D., Widhalm K. ''Effect of 3-Month Treatment of Children and Adolescents with Familial and Polygenic Hypercholesterolaemia with a Soya-Substituted Diet''. *British Journal of Nutrition.* 2008;99:281–286.
118. Laurin D., Jacques H., Moorjani S., Steinke F.H., Gagne C., Brun D., Lupien P.J. ''Effects of a Soy-Protein Beverage on Plasma Lipoproteins in Children with Familial Hypercholesterolemia''. *American Journal of Clinical Nutrition.* 1991;54:98–103.
119. Jacques H., Laurin D., Moorjani S., Steinke F.H., Gagne C., Brun D., Lupien P.J. ''Influence of Diets Containing Cow's Milk or Soy Protein Beverage on Plasma Lipids in Children with Familial Hypercholesterolemia''. *Journal of the American College of Nutrition.* 1992;11 Suppl:69S–73S.
120. Verrillo A., de T.A., Carandente G.P., La R.S. ''Soybean Protein Diets in the Management of Type Ii Hyperlipoproteinaemia''. *Atherosclerosis.* 1985;54:321–331.
121. Huff M.W., Giovannetti P.M., Wolfe B.M. ''Turnover of Very Low-Density Lipoprotein-Apoprotein B Is Increased by Substitution of Soybean Protein for Meat and Dairy Protein in the Diets of Hypercholesterolemic Men''. *American Journal of Clinical Nutrition.* 1984;39:888–897.
122. Wolfe B.M., PM G., CH C., Roberts DC, Carroll K.K. ''Hypolipidemic Effect of Substituting Soybean Protein Isolate for All Meat and Dairy Protein in the Diets of Hypercholesterolemic Men''. *Nutrition Reports International.* 1981;24:1187–1198.
123. Wheeler M.L., Fineberg SE., Fineberg N.S., Gibson R.G., Hackward L.L. ''Animal Versus Plant Protein Meals in Individuals with Type 2 Diabetes and Microalbuminuria: Effects on Renal, Glycemic, and Lipid Parameters''. *Diabetes Care.* 2002;25:1277–1282.
124. Mercer N., Carroll K.K., PM G., FH S., Wolfe B.M. ''Effects of Human Plasma Lipids of Substituting Soybean Protein Isolate for Milk Protein in the Diet''. *Nutrition Reports International.* 1987;35:279–287.
125. D'Amico G., Gentile M.G. ''Effect of Dietary Manipulation on the Lipid Abnormalities and Urinary Protein Loss in Nephrotic Patients''. *Mineral and Electrolyte Metabolism.* 1992;18:203–206.
126. D'Amico G., Gentile M.G., Manna G., Fellin G., Ciceri R., Cofano F., Petrini C., Lavarda F., Perolini S., Porrini M. ''Effect of Vegetarian Soy Diet on Hyperlipidaemia in Nephrotic Syndrome''. *Lancet.* 1992;339:1131–1134.
127. Anderson J.W., Blake J.E., Turner J., Smith B.M. ''Effects of Soy Protein on Renal Function and Proteinuria in Patients with Type 2 Diabetes''. *American Journal of Clinical Nutrition.* 1998;68:1347S–1353S.
128. Soroka N., Silverberg D.S., Greemland M., Birk Y., Blum M., Peer G., Iaina A. ''Comparison of a Vegetable-Based (Soya) and an Animal-Based Low-Protein Diet in Predialysis Chronic Renal Failure Patients''. *Nephron.* 1998;79:173–180.
129. Shige H., Ishikawa T., Higashi K., Yamashita T., Tomiyasu K., Yoshida H., Hosoai H., Ito T., Nakajima K., Ayaori M., Yonemura A., Suzukawa M., Nakamura H. ''Effects of Soy Protein Isolate (Spi) and Casein on the Postprandial Lipemia in Normolipidemic Men''. *Journal of Nutritional Science and Vitaminology.* 1998;44:113–127.
130. Padhi E.M., Blewett H.J., Duncan A.M., Guzman R.P., Hawke A., Seetharaman K., Tsao R., Wolever T.M., Ramdath D.D. ''Whole Soy Flour Incorporated into a Muffin and Consumed at 2 Doses of Soy Protein Does Not Lower Ldl Cholesterol in a Randomized, Double-Blind Controlled Trial of Hypercholesterolemic Adults''. *Journal of Nutrition.* 2015;145:2665–2674.
131. Jenkins D.J., Kendall C.W., Faulkner D., Vidgen E., Trautwein E.A., Parker T.L., Marchie A., Koumbridis G., Lapsley K.G., Josse R.G., Leiter L.A., Connelly P.W. ''A Dietary Portfolio Approach to Cholesterol Reduction: Combined Effects of Plant Sterols, Vegetable Proteins, and Viscous Fibers in Hypercholesterolemia''. *Metabolism.* 2002;51:1596–1604.
132. Jenkins D.J., Kendall C.W., Vidgen E., Mehling C.C., Parker T., Seyler H., Faulkner D., Garsetti M., Griffin L.C., Agarwal S., Rao A.V., Cunnane S.C.,

Ryan M.A., Connelly P.W., Leiter L.A., Vuksan V., Josse R. ''The Effect on Serum Lipids and Oxidized Low-Density Lipoprotein of Supplementing Self-Selected Low-Fat Diets with Soluble-Fiber, Soy, and Vegetable Protein Foods''. *Metabolism.* 2000;49:67–72.

133. Jenkins D.J., Kendall C.W., Garsetti M., Rosenberg-Zand R.S., Jackson C.J., Agarwal S., Rao A.V., Diamandis E.P., Parker T., Faulkner D., Vuksan V., Vidgen E. ''Effect of Soy Protein Foods on Low-Density Lipoprotein Oxidation and Ex Vivo Sex Hormone Receptor Activity—a Controlled Crossover Trial''. *Metabolism.* 2000;49:537–543.
134. Ham J.O., Chapman K.M., Essex-Sorlie D., Bakhit R.M., Prabhudesai M., Winter L.W., Erdman J.W., Jr., Potter S.M. ''Endocrinological Response to Soy Protein and Fiber in Mildly Hypercholesterolemic Men''. *Nutrition Research.* 1993;13:873–884.
135. Roughead Z.K., Hunt J.R., Johnson L.K., Badger T.M., Lykken G.I. ''Controlled Substitution of Soy Protein for Meat Protein: Effects on Calcium Retention, Bone, and Cardiovascular Health Indices in Postmenopausal Women''. *Journal of Clinical Endocrinology and Metabolism.* 2005;90:181–189.
136. Yamashita T., Sasahara T., Pomeroy SE., Collier G., Nestel P.J. ''Arterial Compliance, Blood Pressure, Plasma Leptin, and Plasma Lipids in Women Are Improved with Weight Reduction Equally with a Meat-Based Diet and a Plant-Based Diet''. *Metabolism.* 1998;47:1308–1314.
137. Chen S.T., Ferng S.H., Yang C.S., Peng S.J., Lee H.R., Chen J.R. ''Variable Effects of Soy Protein on Plasma Lipids in Hyperlipidemic and Normolipidemic Hemodialysis Patients''. *American Journal of Kidney Diseases.* 2005;46:1099–1106.
138. Azadbakht L., Shakerhosseini R., Atabak S., Jamshidian M., Mehrabi Y., Esmaill-Zadeh A. ''Beneficiary Effect of Dietary Soy Protein on Lowering Plasma Levels of Lipid and Improving Kidney Function in Type Ii Diabetes with Nephropathy''. *European Journal of Clinical Nutrition.* 2003;57:1292–1294.
139. D'Amico G., Remuzzi G., Maschio G., Gentile M.G., Gotti E., Oldrizzi L., Manna G., Mecca G., Rugiu C., Fellin G. ''Effect of Dietary Proteins and Lipids in Patients with Membranous Nephropathy and Nephrotic Syndrome''. *Clinical Nephrology.* 1991;35:237–242.
140. Liao F.H., Shieh M.J., Yang S.C., Lin S.H., Chien Y.W. ''Effectiveness of a Soy-Based Compared with a Traditional Low-Calorie Diet on Weight Loss and Lipid Levels in Overweight Adults''. *Nutrition.* 2007;23:551–556.
141. Li Z., Hong K., Saltsman P., DeShields S., Bellman M., Thames G., Liu Y., Wang H.J., Elashoff R., Heber D. ''Long-Term Efficacy of Soy-Based Meal Replacements Vs an Individualized Diet Plan in Obese Type Ii Dm Patients: Relative Effects on Weight Loss, Metabolic Parameters, and C-Reactive Protein''. *European Journal of Clinical Nutrition.* 2005;59:411–418.
142. Chiechi L.M., Secreto G., Vimercati A., Greco P., Venturelli E., Pansini F., Fanelli M., Loizzi P., Selvaggi L. ''The Effects of a Soy Rich Diet on Serum Lipids: The Menfis Randomized Trial''. *Maturitas.* 2002;41:97–104.
143. Chiechi L.M., Secreto G., D'Amore M., Fanelli M., Venturelli E., Cantatore F., Valerio T., Laselva G., Loizzi P. ''Efficacy of a Soy Rich Diet in Preventing Postmenopausal Osteoporosis: The Menfis Randomized Trial''. *Maturitas.* 2002;42:295–300.
144. Gentile M.G., Fellin G., Cofano F., Delle F.A., Manna G., Ciceri R., Petrini C., Lavarda F., Pozzi F., D'Amico G. ''Treatment of Proteinuric Patients with a Vegetarian Soy Diet and Fish Oil''. *Clinical Nephrology.* 1993;40:315–320.
145. Vigna G.B., Pansini F., Bonaccorsi G., Albertazzi P., Donega P., Zanotti L., De A.D., Mollica G., Fellin R. ''Plasma Lipoproteins in Soy-Treated Postmenopausal Women: A Double-Blind, Placebo-Controlled Trial''. *Nutrition, Metabolism and Cardiovascular Diseases.* 2000;10:315–322.
146. Zittermann A., Geppert J., Baier S., Zehn N., Gouni-Berthold I., Berthold H.K., Reinsberg J., Stehle P. ''Short-Term Effects of High Soy Supplementation on Sex Hormones, Bone Markers, and Lipid Parameters in Young Female Adults''. *European Journal of Nutrition.* 2004;43:100–108.
147. Cicero A.F., Fiorito A., Panourgia M.P., Sangiorgi Z., Gaddi A. ''Effects of a New Soy/Beta-Sitosterol Supplement on Plasma Lipids in Moderately Hypercholesterolemic Subjects''. *Journal of the Americian Dietetic Association.* 2002;102:1807–1811.
148. Cicero A.F., Minardi M., Mirembe S., Pedro E., Gaddi A. ''Effects of a New Low Dose Soy Protein/Beta-Sitosterol Association on Plasma Lipid Levels and Oxidation''. *European Journal of Nutrition.* 2004;43:319–322.
149. Lukaczer D., Liska D.J., Lerman R.H., Darland G., Schiltz B., Tripp M., Bland J.S. ''Effect of a Low Glycemic Index Diet with Soy Protein and Phytosterols on Cvd Risk Factors in Postmenopausal Women''. *Nutrition.* 2006;22:104–113.
150. Jenkins D.J., Kendall C.W., Marchie A., Faulkner D., Vidgen E., Lapsley K.G., Trautwein E.A., Parker T.L., Josse R.G., Leiter L.A., Connelly P.W. ''The Effect of Combining Plant Sterols, Soy Protein, Viscous Fibers, and Almonds in Treating Hypercholesterolemia''. *Metabolism.* 2003;52:1478–1483.
151. Jenkins D.J., Kendall C.W., Marchie A., Faulkner D.A., Wong J.M., de Souza R., Emam A., Parker T.L., Vidgen E., Lapsley K.G., Trautwein E.A., Josse R.G., Leiter L.A., Connelly P.W. ''Effects of a Dietary Portfolio of Cholesterol-Lowering Foods Vs Lovastatin on Serum Lipids and C-Reactive Protein''. *Journal of the American Medical Association.* 2003;290:502–510.
152. Jenkins D.J., Kendall C.W., Faulkner D.A., Nguyen T., Kemp T., Marchie A., Wong J.M., de Souza R., Emam A., Vidgen E., Trautwein E.A., Lapsley K.G., Holmes C., Josse R.G., Leiter L.A., Connelly P.W., Singer W. ''Assessment of the Longer-Term Effects of a Dietary Portfolio of Cholesterol-Lowering Foods in Hypercholesterolemia''. *American Journal of Clinical Nutrition.* 2006;83:582–591.
153. Jenkins D.J., Kendall C.W., Marchie A., Faulkner D.A., Wong J.M., de Souza R., Emam A., Parker T.L., Vidgen E., Trautwein E.A., Lapsley K.G., Josse R.G., Leiter L.A., Singer W., Connelly P.W. ''Direct Comparison of a Dietary Portfolio of Cholesterol-Lowering Foods with a Statin in Hypercholesterolemic Participants''. *American Journal of Clinical Nutrition.* 2005;81:380–387.
154. Jenkins D.J., Kendall C.W., Marchie A., Faulkner D.A., Josse A.R., Wong J.M., de Souza R., Emam A., Parker T.L., Li T.J., Josse R.G., Leiter L.A., Singer W., Connelly P.W. ''Direct Comparison of Dietary Portfolio Vs Statin on C-Reactive Protein''. *European Journal of Clinical Nutrition.* 2005;59:851–860.
155. Jones P.J., Raeini-Sarjaz M., Jenkins D.J., Kendall C.W., Vidgen E., Trautwein E.A., Lapsley K.G., Marchie A., Cunnane S.C., Connelly P.W. ''Effects of a Diet High in Plant Sterols, Vegetable Proteins, and Viscous Fibers (Dietary Portfolio) on Circulating Sterol Levels and Red Cell Fragility in Hypercholesterolemic Subjects''. *Lipids.* 2005;40:169–174.
156. National Heart L., and Blood Institute. ''Clinical Guidelines on Cholesterol Management in Adults (Atp Iii)—'', NIH Publication No. 02–5215. 2002.
157. James P.A., Oparil S., Carter B.L., Cushman W.C., Dennison-Himmelfarb C., Handler J., Lackland D.T., LeFevre M.L., MacKenzie T.D., Ogedegbe O., Smith S.C., Jr., Svetkey L.P., Taler S.J., Townsend R.R., Wright J.T., Jr., Narva A.S., Ortiz E. ''2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (Jnc 8)''. *Journal of the American Medical Association.* 2014;311:507–520.
158. National Heart L.a.B.I. ''Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure'', NIH Publication No. 03–5233. 2003.
159. Carmignani L.O., Pedro A.O., da Costa-Paiva L.H., Pinto-Neto A.M. ''The Effect of Soy Dietary Supplement and Low Dose of Hormone Therapy on Main Cardiovascular Health Biomarkers: A Randomized Controlled Trial''. *Revista Brasileira de Ginecologia e Obstetricia.* 2014;36:251–258.
160. Liu Z.M., Ho S.C., Chen Y.M., Ho Y.P. ''The Effects of Isoflavones Combined with Soy Protein on Lipid Profiles, C-Reactive Protein and Cardiovascular Risk among Postmenopausal Chinese Women''. *Nutrition, Metabolism and Cardiovascular Diseases.* 2012;22:712–719.
161. Santo A.S., Cunningham A.M., Alhassan S., Browne R.W., Burton H., Leddy J.J., Grandjean P.W., Horvath S.M., Horvath

P.J. ''Nmr Analysis of Lipoprotein Particle Size Does Not Increase Sensitivity to the Effect of Soy Protein on Cvd Risk When Compared with the Traditional Lipid Profile''. *Applied Physiology, Nutrition, and Metabolism.* 2008;33:489–500.
162. Evans M., Njike V.Y., Hoxley M., Pearson M., Katz D.L. ''Effect of Soy Isoflavone Protein and Soy Lecithin on Endothelial Function in Healthy Postmenopausal Women''. *Menopause.* 2007;14:141–149.
163. Maesta N., Nahas E.A., Nahas-Neto J., Orsatti F.L., Fernandes C.E., Traiman P., Burini R.C. ''Effects of Soy Protein and Resistance Exercise on Body Composition and Blood Lipids in Postmenopausal Women''. *Maturitas.* 2007;56:350–358.
164. Kohno M., Hirotsuka M., Kito M., Matsuzawa Y. ''Decreases in Serum Triacylglycerol and Visceral Fat Mediated by Dietary Soybean Beta-Conglycinin''. *Journal of Atherosclerosis and Thrombosis.* 2006;13:247–255.
165. McVeigh B.L., Dillingham B.L., Lampe J.W., Duncan A.M. ''Effect of Soy Protein Varying in Isoflavone Content on Serum Lipids in Healthy Young Men''. *American Journal of Clinical Nutrition.* 2006;83:244–251.
166. Sagara M., Kanda T., NJelekera M., Teramoto T., Armitage L., Birt N., Birt C., Yamori Y. ''Effects of Dietary Intake of Soy Protein and Isoflavones on Cardiovascular Disease Risk Factors in High Risk, Middle-Aged Men in Scotland''. *Journal of the American College of Nutrition.* 2004;23:85–91.
167. Teixeira S.R., Tappenden K.A., Carson L., Jones R., Prabhudesai M., Marshall W.P., Erdman J.W., Jr. ''Isolated Soy Protein Consumption Reduces Urinary Albumin Excretion and Improves the Serum Lipid Profile in Men with Type 2 Diabetes Mellitus and Nephropathy''. *Journal of Nutrition.* 2004;134:1874–1880.
168. Murray M.J., Meyer W.R., Lessey B.A., Oi R.H., DeWire R.E., Fritz M.A. ''Soy Protein Isolate with Isoflavones Does Not Prevent Estradiol-Induced Endometrial Hyperplasia in Postmenopausal Women: A Pilot Trial''. *Menopause.* 2003;10:456–464.
169. Jayagopal V., Albertazzi P., Kilpatrick E.S., Howarth E.M., Jennings P.E., Hepburn D.A., Atkin S.L. ''Beneficial Effects of Soy Phytoestrogen Intake in Postmenopausal Women with Type 2 Diabetes''. *Diabetes Care.* 2002;25:1709–1714.
170. Teede H.J., Dalais F.S., Kotsopoulos D., Liang Y.L., Davis S., McGrath B.P. ''Dietary Soy Has Both Beneficial and Potentially Adverse Cardiovascular Effects: A Placebo-Controlled Study in Men and Postmenopausal Women''. *Journal of Clinical Endocrinology and Metabolism.* 2001;86:3053–3060.
171. Dalais F.S., Ebeling P.R., Kotsopoulos D., McGrath B.P., Teede H.J. ''The Effects of Soy Protein Containing Isoflavones on Lipids and Indices of Bone Resorption in Postmenopausal Women''. *Clinical Endocrinology.* 2003;58:704–709.
172. Washburn S., Burke G.L., Morgan T., Anthony M. ''Effect of Soy Protein Supplementation on Serum Lipoproteins, Blood Pressure, and Menopausal Symptoms in Perimenopausal Women''. *Menopause.* 1999;6:7–13.
173. Gooderham M.H., Adlercreutz H., Ojala S.T., Wahala K., Holub B.J. ''A Soy Protein Isolate Rich in Genistein and Daidzein and Its Effects on Plasma Isoflavone Concentrations, Platelet Aggregation, Blood Lipids and Fatty Acid Composition of Plasma Phospholipid in Normal Men''. *Journal of Nutrition.* 1996;126:2000–2006.
174. Mangano K.M., Hutchins-Wiese H.L., Kenny A.M., Walsh S.J., Abourizk R.H., Bruno R.S., Lipcius R., Fall P., Kleppinger A., Kenyon-Pesce L., Prestwood K.M., Kerstetter J.E. ''Soy Proteins and Isoflavones Reduce Interleukin-6 but Not Serum Lipids in Older Women: A Randomized Controlled Trial''. *Nutrition Research.* 2013;33:1026–1033.
175. Steinberg F.M., Guthrie N.L., Villablanca A.C., Kumar K., Murray M.J. ''Soy Protein with Isoflavones Has Favorable Effects on Endothelial Function That Are Independent of Lipid and Antioxidant Effects in Healthy Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2003;78:123–130.
176. Bakhit R.M., Klein B.P., Essex-Sorlie D., Ham J.O., Erdman J.W., Jr., Potter S.M. ''Intake of 25 G of Soybean Protein with or without Soybean Fiber Alters Plasma Lipids in Men with Elevated Cholesterol Concentrations''. *Journal of Nutrition.* 1994;124:213–222.
177. van Raaij J.M., Katan M.B., Hautvast J.G., Hermus R.J. ''Effects of Casein Versus Soy Protein Diets on Serum Cholesterol and Lipoproteins in Young Healthy Volunteers''. *American Journal of Clinical Nutrition.* 1981;34:1261–1271.
178. Takatsuka N., Nagata C., Kurisu Y., Inaba S., Kawakami N., Shimizu H. ''Hypocholesterolemic Effect of Soymilk Supplementation with Usual Diet in Premenopausal Normolipidemic Japanese Women''. *Preventive Medicine.* 2000;31:308–314.
179. Mitchell J.H., Collins A.R. ''Effects of a Soy Milk Supplement on Plasma Cholesterol Levels and Oxidative DNA Damage in Men—a Pilot Study''. *European Journal of Nutrition.* 1999;38:143–148.
180. Murkies A.L., Lombard C., Strauss B.J., Wilcox G., Burger H.G., Morton M.S. ''Dietary Flour Supplementation Decreases Post-Menopausal Hot Flushes: Effect of Soy and Wheat''. *Maturitas.* 1995;21:189–195.
181. Matthan N.R., Jalbert S.M., Ausman L.M., Kuvin J.T., Karas R.H., Lichtenstein A.H. ''Effect of Soy Protein from Differently Processed Products on Cardiovascular Disease Risk Factors and Vascular Endothelial Function in Hypercholesterolemic Subjects''. *American Journal of Clinical Nutrition.* 2007;85:960–966.
182. Jenkins D.J., Wolever T.M., Spiller G., Buckley G., Lam Y., Jenkins A.L., Josse R.G. ''Hypocholesterolemic Effect of Vegetable Protein in a Hypocaloric Diet''. *Atherosclerosis.* 1989;78:99–107.
183. Bosello O., Cominacini L., Zocca I., Garbin U., Compri R., Davoli A., Brunetti L. ''Short- and Long-Term Effects of Hypocaloric Diets Containing Proteins of Different Sources on Plasma Lipids and Apoproteins of Obese Subjects''. *Annals of Nutrition and Metabolism.* 1988;32:206–214.
184. Greany K.A., Nettleton J.A., Wangen K.E., Thomas W., Kurzer M.S. ''Probiotic Consumption Does Not Enhance the Cholesterol-Lowering Effect of Soy in Postmenopausal Women''. *Journal of Nutrition.* 2004;134:3277–3283.
185. Wong W.W., Smith E.O., Stuff J.E., Hachey D.L., Heird W.C., Pownell H.J. ''Cholesterol-Lowering Effect of Soy Protein in Normocholesterolemic and Hypercholesterolemic Men''. *American Journal of Clinical Nutrition.* 1998;68:1385S–1389S.
186. Goldberg A.P., Lim A., Kolar J.B., Grundhauser J.J., Steinke F.H., Schonfeld G. ''Soybean Protein Independently Lowers Plasma Cholesterol Levels in Primary Hypercholesterolemia''. *Atherosclerosis.* 1982;43:355–368.
187. Hoie L.H., Guldstrand M., Sjoholm A., Graubaum H.J., Gruenwald J., Zunft H.J., Lueder W. ''Cholesterol-Lowering Effects of a New Isolated Soy Protein with High Levels of Nondenaturated Protein in Hypercholesterolemic Patients''. *Advances in Therapy.* 2007;24:439–447.
188. Hoie L.H., Sjoholm A., Guldstrand M., Zunft H.J., Lueder W., Graubaum H.J., Gruenwald J. ''Ultra Heat Treatment Destroys Cholesterol-Lowering Effect of Soy Protein''. *International Journal of Food Sciences and Nutrition.* 2006;57:512–519.
189. Hoie L.H., Morgenstern E.C., Gruenwald J., Graubaum H.J., Busch R., Luder W., Zunft H.J. ''A Double-Blind Placebo-Controlled Clinical Trial Compares the Cholesterol-Lowering Effects of Two Different Soy Protein Preparations in Hypercholesterolemic Subjects''. *European Journal of Nutrition.* 2005;44:65–71.
190. Hoie L.H., Graubaum H.J., Harde A., Gruenwald J., Wernecke K.D. ''Lipid-Lowering Effect of 2 Dosages of a Soy Protein Supplement in Hypercholesterolemia''. *Advances in Therapy.* 2005;22:175–186.
191. Teede H.J., Dalais F.S., Kotsopoulos D., McGrath B.P., Malan E., Gan T.E., Peverill R.E. ''Dietary Soy Containing Phytoestrogens Does Not Activate the Hemostatic System in Postmenopausal Women''. *Journal of Clinical Endocrinology and Metabolism.* 2005;90:1936–1941.
192. Harrison R.A., Sagara M., Rajpura A., Armitage L., Birt N., Birt C.A., Yamori Y. ''Can Foods with Added Soya-Protein or Fish-Oil Reduce Risk Factors for Coronary Disease? A Factorial Randomised Controlled Trial''. *Nutrition, Metabolism and Cardiovascular Diseases.* 2004;14:344–350.

193. Blum A., Lang N., Vigder F., Israeli P., Gumanovsky M., Lupovitz S., Elgazi A., Peleg A., Ben-Ami M. ''Effects of Soy Protein on Endothelium-Dependent Vasodilatation and Lipid Profile in Postmenopausal Women with Mild Hypercholesterolemia''. *Clinical Investigative Medicine.* 2003;26:20–26.
194. Cuevas A.M., Irribarra V.L., Castillo O.A., Yanez M.D., Germain A.M. ''Isolated Soy Protein Improves Endothelial Function in Postmenopausal Hypercholesterolemic Women''. *European Journal of Clinical Nutrition.* 2003;57:889–894.
195. Gardner C.D., Newell K.A., Cherin R., Haskell W.L. ''The Effect of Soy Protein with or without Isoflavones Relative to Milk Protein on Plasma Lipids in Hypercholesterolemic Postmenopausal Women''. *American Journal of Clinical Nutrition.* 2001;73:728–735.
196. Hori G., Wang M.F., Chan Y.C., Komatsu T., Wong Y., Chen T.H., Yamamoto K., Nagaoka S., Yamamoto S. ''Soy Protein Hydrolyzate with Bound Phospholipids Reduces Serum Cholesterol Levels in Hypercholesterolemic Adult Male Volunteers''. *Bioscience, Biotechnology, and Biochemistry.* 2001;65:72–78.
197. Chen S.T., Chen J.R., Yang C.S., Peng S.J., Ferng S.H. ''Effect of Soya Protein on Serum Lipid Profile and Lipoprotein Concentrations in Patients Undergoing Hypercholesterolaemic Haemodialysis''. *British Journal of Nutrition.* 2006;95:366–371.
198. Ma Y., Chiriboga D., Olendzki B.C., Nicolosi R., Merriam P.A., Ockene I.S. ''Effect of Soy Protein Containing Isoflavones on Blood Lipids in Moderately Hypercholesterolemic Adults: A Randomized Controlled Trial''. *Journal of the American College of Nutrition.* 2005;24:275–285.
199. West S.G., Hilpert K.F., Juturu V., Bordi P.L., Lampe J.W., Mousa S.A., Kris-Etherton P.M. ''Effects of Including Soy Protein in a Blood Cholesterol-Lowering Diet on Markers of Cardiac Risk in Men and in Postmenopausal Women with and without Hormone Replacement Therapy''. *Journal of Womens Health.* 2005;14:253–262.
200. Hilpert K.F., Kris-Etherton P.M., West S.G. ''Lipid Response to a Low-Fat Diet with or without Soy Is Modified by C-Reactive Protein Status in Moderately Hypercholesterolemic Adults''. *Journal of Nutrition.* 2005;135:1075–1079.
201. Jenkins D.J., Kendall C.W., Jackson C.J., Connelly P.W., Parker T., Faulkner D., Vidgen E., Cunnane S.C., Leiter L.A., Josse R.G. ''Effects of High- and Low-Isoflavone Soyfoods on Blood Lipids, Oxidized Ldl, Homocysteine, and Blood Pressure in Hyperlipidemic Men and Women''. *American Journal of Clinical Nutrition.* 2002;76:365–372.
202. Jenkins D.J., Kendall C.W., Connelly P.W., Jackson C.J., Parker T., Faulkner D., Vidgen E. ''Effects of High- and Low-Isoflavone (Phytoestrogen) Soy Foods on Inflammatory Biomarkers and Proinflammatory Cytokines in Middle-Aged Men and Women''. *Metabolism.* 2002;51:919–924.
203. Lichtenstein A.H., Jalbert S.M., Adlercreutz H., Goldin B.R., Rasmussen H., Schaefer E.J., Ausman L.M. ''Lipoprotein Response to Diets High in Soy or Animal Protein with and without Isoflavones in Moderately Hypercholesterolemic Subjects''. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2002;22:1852–1858.
204. Wang Y., Jones P.J., Ausman L.M., Lichtenstein A.H. ''Soy Protein Reduces Triglyceride Levels and Triglyceride Fatty Acid Fractional Synthesis Rate in Hypercholesterolemic Subjects''. *Atherosclerosis.* 2004;173:269–275.
205. Desroches S., Mauger J.F., Ausman L.M., Lichtenstein A.H., Lamarche B. ''Soy Protein Favorably Affects Ldl Size Independently of Isoflavones in Hypercholesterolemic Men and Women''. *Journal of Nutrition.* 2004;134:574–579.
206. Van H.L., Liu K., Gerber J., Garside D., Schiffer L., Gernhofer N., Greenland P. ''Oats and Soy in Lipid-Lowering Diets for Women with Hypercholesterolemia: Is There Synergy?''. *Journal of the American Dietetic Association.* 2001;101:1319–1325.
207. Gardner C.D., Messina M., Kiazand A., Morris J.L., Franke A.A. ''Effect of Two Types of Soy Milk and Dairy Milk on Plasma Lipids in Hypercholesterolemic Adults: A Randomized Trial''. *Journal of the American College of Nutrition.* 2007;26:669–677.
208. Jenkins D.J., Kendall C.W., Vidgen E., Vuksan V., Jackson C.J., Augustin L.S., Lee B., Garsetti M., Agarwal S., Rao A.V., Cagampang G.B., Fulgoni V., III. ''Effect of Soy-Based Breakfast Cereal on Blood Lipids and Oxidized Low-Density Lipoprotein''. *Metabolism.* 2000;49:1496–1500.
209. Teede H.J., Giannopoulos D., Dalais F.S., Hodgson J., McGrath B.P. ''Randomised, Controlled, Cross-over Trial of Soy Protein with Isoflavones on Blood Pressure and Arterial Function in Hypertensive Subjects''. *Journal of the American College of Nutrition.* 2006;25:533–540.
210. Burke V., Hodgson J.M., Beilin L.J., Giangiulioi N., Rogers P., Puddey I.B. ''Dietary Protein and Soluble Fiber Reduce Ambulatory Blood Pressure in Treated Hypertensives''. *Hypertension.* 2001;38:821–826.
211. Jenkins D.J., Kendall C.W., Faulkner D.A., Kemp T., Marchie A., Nguyen T.H., Wong J.M., de Souza R., Emam A., Vidgen E., Trautwein E.A., Lapsley K.G., Josse R.G., Leiter L.A., Singer W. ''Long-Term Effects of a Plant-Based Dietary Portfolio of Cholesterol-Lowering Foods on Blood Pressure''. *European Journal of Clinical Nutrition.* 2008;62:781–788.
212. He J., Gu D., Wu X., Chen J., Duan X., Chen J., Whelton P.K. ''Effect of Soybean Protein on Blood Pressure: A Randomized, Controlled Trial''. *Annals of Internal Medicine.* 2005;143:1–9.
213. Rivas M., Garay R.P., Escanero J.F., Cia P., Jr., Cia P., Alda J.O. ''Soy Milk Lowers Blood Pressure in Men and Women with Mild to Moderate Essential Hypertension''. *Journal of Nutrition.* 2002;132:1900–1902.
214. Chan Y.H., Lau K.K., Yiu K.H., Li S.W., Chan H.T., Tam S., Shu X.O., Lau C.P., Tse H.F. ''Isoflavone Intake in Persons at High Risk of Cardiovascular Events: Implications for Vascular Endothelial Function and the Carotid Atherosclerotic Burden''. *American Journal of Clinical Nutrition.* 2007;86:938–945.
215. Ho S.C., Woo J.L., Leung S.S., Sham A.L., Lam T.H., Janus E.D. ''Intake of Soy Products Is Associated with Better Plasma Lipid Profiles in the Hong Kong Chinese Population''. *Journal of Nutrition.* 2000;130:2590–2593.
216. Ho S.Y., Schooling M., Hui L.L., McGhee S.M., Mak K.H., Lam T.H. ''Soy Consumption and Mortality in Hong Kong: Proxy-Reported Case-Control Study of All Older Adult Deaths in 1998''. *Preventive Medicine.* 2006;43:20–26.
217. Kokubo Y., Iso H., Ishihara J., Okada K., Inoue M., Tsugane S., Group J.S. ''Association of Dietary Intake of Soy, Beans, and Isoflavones with Risk of Cerebral and Myocardial Infarctions in Japanese Populations: The Japan Public Health Center-Based (Jphc) Study Cohort I''. *Circulation.* 2007;116:2553–2562.
218. Nagata C., Shimizu H., Takami R., Hayashi M., Takeda N., Yasuda K. ''Soy Product Intake Is Inversely Associated with Serum Homocysteine Level in Premenopausal Japanese Women''. *Journal of Nutrition.* 2003;133:797–800.
219. Nagata C., Takatsuka N., Kurisu Y., Shimizu H. ''Decreased Serum Total Cholesterol Concentration Is Associated with High Intake of Soy Products in Japanese Men and Women''. *Journal of Nutrition.* 1998;128:209–213.
220. Rosell M.S., Appleby P.N., Spencer E.A., Key T.J. ''Soy Intake and Blood Cholesterol Concentrations: A Cross-Sectional Study of 1033 Pre- and Postmenopausal Women in the Oxford Arm of the European Prospective Investigation into Cancer and Nutrition''. *American Journal of Clinical Nutrition.* 2004;80:1391–1396.
221. Sasazuki S., Fukuoka Heart Study G. ''Case-Control Study of Nonfatal Myocardial Infarction in Relation to Selected Foods in Japanese Men and Women''. *Jpn Circ J.* 2001;65:200–206.
222. Yang G., Shu X.O., Jin F., Zhang X., Li H.L., Li Q., Gao Y.T., Zheng W. ''Longitudinal Study of Soy Food Intake and Blood Pressure among Middle-Aged and Elderly Chinese Women''. *American Journal of Clinical Nutrition.* 2005;81:1012–1017.
223. Zhang B., Chen Y.M., Huang L.L., Zhou X.X., Chen C.G., Ye Y.B., Su Y.X. ''Greater Habitual Soyfood Consumption Is Associated with Decreased Carotid Intima-Media Thickness and Better Plasma Lipids in Chinese Middle-Aged Adults''. *Atherosclerosis.* 2008;198:403–411.
224. Zhang X., Shu X.O., Gao Y.T., Yang G., Li Q., Li H., Jin F., Zheng W. ''Soy Food Consumption Is Associated with Lower Risk of Coronary Heart Disease in

Chinese Women''. *Journal of Nutrition.* 2003;133:2874–2878.
225. Flegal K.M. ''Evaluating Epidemiologic Evidence of the Effects of Food and Nutrient Exposures''. *American Journal of Clinical Nutrition.* 1999;69:1339S–1344S.
226. Lichtenstein A.H., Russell R.M. ''Essential Nutrients: Food or Supplements? Where Should the Emphasis Be?''. *Journal of the American Medical Association.* 2005;294:351–358.
227. Peto R., Doll R., Buckley J.D., Sporn M.B. ''Can Dietary Beta-Carotene Materially Reduce Human Cancer Rates?''. *Nature.* 1981;290:201–208.
228. ''The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group''. *New England Journal of Medicine.* 1994;330:1029–1035.
229. Omenn G.S., Goodman G.E., Thornquist M.D., Balmes J., Cullen M.R., Glass A., Keogh J.P., Meyskens F.L., Valanis B., Williams J.H., Barnhart S., Hammar S. ''Effects of a Combination of Beta Carotene and Vitamin a on Lung Cancer and Cardiovascular Disease''. *New England Journal of Medicine.* 1996;334:1150–1155.
230. Food and Drug Administration, ''Tables of Scientific Evidence Regarding the Relationship Between Soy Protein and CHD''

List of Subjects in 21 CFR Part 101

Food labeling, 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 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; 42 U.S.C. 243, 264, 271.

§ 101.82 [Removed]

■ 2. Remove § 101.82.

Dated: October 26, 2017.

Anna K. Abram,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

[FR Doc. 2017–23629 Filed 10–30–17; 8:45 am]

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POSTAL SERVICE

39 CFR Part 111

eInduction Option, Seamless Acceptance Program, and Full-Service Automation Option, Verification Standards

AGENCY: Postal Service™.

ACTION: Proposed rule.

SUMMARY: The Postal Service is proposing to amend *Mailing Standards of the United States Postal Service,* Domestic Mail Manual (DMM®), sections 705.20, *eInduction Option,* 705.22, *Seamless Acceptance Program,* and 705.23, *Full-Service Automation Option,* to add the verification standards.

DATES: Submit comments on or before November 30, 2017.

ADDRESSES: Mail or deliver written comments to the manager, Product Classification, U.S. Postal Service, 475 L'Enfant Plaza SW., Room 4446, Washington, DC 20260–5015. If sending comments by email, include the name and address of the commenter and send to *ProductClassification@usps.gov,* with a subject line of ''Verification Standards''. Faxed comments are not accepted. You may inspect and photocopy all written comments, by appointment only, at USPS® Headquarters Library, 475 L'Enfant Plaza SW., 11th Floor North, Washington, DC 20260. These records are available for review on Monday through Friday, 9 a.m.–4 p.m., by calling 202–268–2906.

FOR FURTHER INFORMATION CONTACT: Heather Dyer at (207) 482–7217, or Garry Rodriguez at (202) 268–7281.

SUPPLEMENTARY INFORMATION: The Postal Service is proposing to amend DMM sections 705.20, *eInduction Option,* 705.22, *Seamless Acceptance Program,* and 705.23, *Full-Service Automation Option,* to add the applicable verification descriptions, error thresholds, and postage assessments, standards. These standards have been made available to the public via Publication 6850, *Publication for Streamlined Mail Acceptance for Letters and Flats,* available at *https://postalpro.usps.com,* which also contains additional information on the verification processes.

List of Subjects in 39 CFR Part 111

Administrative practice and procedure, Postal Service.

Although we are exempt from the notice and comment requirements of the Administrative Procedure Act (5 U.S.C. 553(b), (c)) regarding proposed rulemaking by 39 U.S.C. 410(a), we invite public comments on the following proposed revisions to *Mailing Standards of the United States Postal Service,* Domestic Mail Manual (DMM), incorporated by reference in the Code of Federal Regulations. *See* 39 CFR 111.1. Accordingly, 39 CFR part 111 is proposed to be amended as follows:

PART 111—[AMENDED]

■ 1. The authority citation for 39 CFR part 111 continues to read as follows:

Authority: 5 U.S.C. 552(a); 13 U.S.C. 301–307; 18 U.S.C. 1692–1737; 39 U.S.C. 101, 401, 403, 404, 414, 416, 3001–3011, 3201–3219, 3403–3406, 3621, 3622, 3626, 3632, 3633, and 5001.

■ 2. Revise the following sections of *Mailing Standards of the United States Postal Service,* Domestic Mail Manual (DMM), as follows:

Mailing Standards of the United States Postal Service, Domestic Mail Manual (DMM)

* * * * *

700 Special Standards

* * * * *

705 Advanced Preparation and Special Postage Payment Systems

* * * * *

705.20.0 eInduction Option

20.1 Description

[Revise the fourth sentence of 20.1 to read as follows:]

* * * For additional information on the eInduction Option see Publication 6850, *Publication for Streamlined Mail Acceptance for Letters and Flats,* available at *https://postalpro.usps.com.*

* * * * *

[Add new subsection 20.5, Verifications, to read as follows:]

20.5 Verifications

The six eInduction option verification descriptions, error thresholds, and postage assessments, are provided in 20.5.1 through 20.5.6.

20.5.1 Undocumented (Extra) Containers Verification

An Undocumented Container error occurs when a scanned IMcb is not found in an eDoc, or is included in an eDoc and associated to a postage statement in estimated (EST) status. Containers will be flagged as Undocumented 10 days after the scan unload date/time if no eDoc has been uploaded or if the postage statement is still in EST status. The threshold is 0%. All errors will be subject to an