21 CFR Part 101

[Docket No. 91N-0095]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements; Lipids and Cardiovascular Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to authorize the use on foods and food labeling of health claims relating to the association between reduction in dietary intake of lipids (particularly saturated fats and cholesterol), decreased blood cholesterol, and decreased risk of cardiovascular disease, particularly coronary heart disease. The agency reviewed this topic under provisions of the Nutrition Labeling and Education Act of 1990. The agency's conclusion is based on its review of the available scientific literature and on its review of conclusions and recommendations provided by the Federal government and other documents from recognized scientific bodies. The agency concludes that the strength and consistency of the extensive publicly available scientific evidence supports such claims, and that there is significant scientific agreement, among experts qualified by scientific training and experience, to evaluate such claims, about such support.

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

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Paddy Wiesenfeld, Center for Food Safety and Applied Nutrition (HFF-268), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-245-1492.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Nutrition Labeling and Education Act of 1990

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

Published elsewhere in this issue of the Federal Register is a proposed rulemaking to establish general requirements pertaining to the use on food labels and in labeling of health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs, or other nutritional substances (referred to generally as "substances"), to a disease or health-related condition (proposed in "General Principles for Health Claims"). In the proposal on general requirements for health claims, FDA, following the provisions of the 1990 amendments, has tentatively determined that for foods that qualify for claims, such claims would only be justified for substances in dietary supplements as well as in conventional foods if the agency determines based on the totality of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles) that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The 1990 amendments also require (section 3(b)(1)(A)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x) that within 12 months of their enactment, the Secretary shall issue proposed regulations to implement section 403(r) of the act, and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including lipids and cardiovascular disease, meet the requirements of the act. In this document, the agency will consider whether a claim on food or food products, including conventional foods and dietary supplements, on the relationship between lipids and cardiovascular disease would be justified under the standard proposed in "Food Labeling: General Requirements for Health Claims for Food."

B. Public Health Aspects: Basis for Considering a Health Claim Relating Lipids and Cardiovascular Disease

1. Cardiovascular Disease

The specific disease or health related condition identified in the 1990 amendments is cardiovascular disease, diseases of the heart and blood vessels. Cardiovascular disease is a major public health problem in the United States. Coronary heart disease (CHD) is the most common, most frequently reported and most serious form of cardiovascular disease. Despite the dramatic decline over the past 15 years in the death rate from cardiovascular disease: 35 percent for all cardiovascular disease, 49 percent for CHD, and more than 50 percent for stroke (Ref. 36), CHD and stroke kill nearly as many Americans as all other diseases combined. Cardiovascular disease, primarily CHD, is also among the leading causes of disability. Changes in lifestyles, risk factor reduction, and medical intervention were major contributors to this decline (Ref. 36).

In order to be consistent with the magnitude of the public health problem and with the conclusions of the Federal government and other reports from recognized scientific bodies, such as the National Research Council (Ref. 20) and the Life Sciences Research Office (LSRO) (Ref. 78), the focus of this document is CHD rather than the broader problem of cardiovascular disease. CHD is the most common, most serious, and earliest form of cardiovascular disease, frequently producing symptoms and health problems in middle-aged adults (Ref. 20). Despite a declining death rate from CHD since the mid 1960's, CHD still accounts for more deaths than any other disease or group of diseases (Ref. 35). More than 1.25 million heart attacks occur each year (two-thirds occur in men), and more than 500,000 people die as a result (Ref. 35). In the United States, it is very common for significant pathogenesis of CHD to occur without easily detectable symptoms (Refs. 31 through 34). Thus, the total affected population is considerably larger than the statistics on death and illness would indicate. In addition to its impact on the nation's health, CHD costs the U.S. economy over $50 billion annually (Ref. 35).

2. Dietary Lipids

Food sources of dietary lipids commonly consumed in the United States include fats and oils (e.g., butter, margarine, vegetable oils, and shortenings), salad dressings, meats, and whole dairy products and egg yolk,

Digestion of food fats liberates fatty acids and other lipid components, including cholesterol, that are then absorbed for use in the body.

Fatty acids may be classified by length: short-chain (less than 6 carbons), medium-chain (6 to 10 carbons), or long-chain (12 or more carbons). Fatty acids may also be classified as saturated fatty acids (lacking double bonds), as monounsaturated fatty acids (containing one double bond), or as polyunsaturated fatty acids (containing two or more double bonds). The polyunsaturated fatty acids are subdivided into those whose first double bond occurs either three carbon atoms from the methyl end (omega-6-fatty acids) or six carbon atoms from the methyl end (omega-3-fatty acids) of the molecule. Dietary lipids and fatty acids are commonly referred to as "fat," e.g., as "total dietary fat" and as "saturated fat or saturated fatty acid" or "polyunsaturated fat or polyunsaturated fatty acid."

Dietary fats serve several major physiological functions. Small amounts (1 to 2 percent of total calories) of linoleic and linoleic acids, two polyunsaturated fatty acids, are essential in the diet as precursors of other essential lipids. Fats facilitate the intestinal absorption of fat-soluble vitamins. Cholesterol and other lipids are major components of all cell membranes. In addition, cholesterol is the precursor for synthesis of steroid hormones and bile acids.

Fat is the most concentrated source of dietary energy of all the nutrients, supplying 9 calories per gram (g) as compared to 4 calories per g from either carbohydrate or protein. More than one-third of the calories consumed by most people in the United States are provided by fat. In 1985, the estimated average intake of total fat ranged from 34 percent of caloric intake for children 1 to 5 years of age to 37 percent of calories for adults 19 to 50 years of age (Ref. 107). On average, saturated fat intakes were between 13 to 14 percent of calories. The major dietary sources of both total and saturated fats were dairy and meat products and baked goods.

Dietary cholesterol is also a type of dietary lipid, but it has different chemical and physiological properties from fatty acids. Cholesterol is derived either from the diet or from synthesis in the body. Only about 40 percent of ingested cholesterol is absorbed, the remaining 60 percent passes out in the stool. Average daily intakes of dietary cholesterol in the United States are estimated to be 304 milligrams (mg) and 435 mg for women and men, respectively (Refs. 20 and 33).

3. Relationship of Dietary Lipid (Saturated Fats and Cholesterol) and CHD

Because of the importance of CHD as a public health problem, identification of "modifiable" risk factors has received considerable research and public health policy attention since the early part of this century. Fatty streaks and cholesterol were identified many years ago as prominent components of the blood vessel (arterial) lesions whose buildup caused a narrowing or blockage of the blood flow to the heart (Refs. 20, 33, and 35). Following these early observations, a large body of scientific evidence has accumulated on the relationship of different types and amounts of dietary fats to risk of CHD. Based on the weight of the scientific evidence now available, virtually all recent dietary guidelines for Americans, whether from the Federal government or from the community of health professionals, have noted the high intake of dietary fat by the U.S. population and also the strong association of diets high in fat, particularly saturated fat and cholesterol, with increased risk of CHD (Refs. 20, 29, 31, 32, 33, 34, 35, and 36).

Many risk factors contribute to development of CHD. There is general agreement that elevated blood cholesterol levels are one of the major "modifiable" risk factors in the development of CHD (Refs. 31, 32, 35, and 36). Federal government and other reviews (Refs. 20, 31, and 33 through 36) concluded that there is substantial epidemiologic and clinical evidence that high blood levels of total cholesterol and low density lipoprotein cholesterol (LDL-cholesterol; LDL–C) are a cause of atherosclerosis (inadequate circulation of blood to the heart due to narrowing of the arteries), and represent major contributors to CHD (Refs. 20, and 31 through 36). Factors that decrease total blood cholesterol and LDL-cholesterol will also decrease the risk of CHD. High intakes of saturated fat, and to a lesser degree, of dietary cholesterol are consistently associated with elevated blood cholesterol levels. Thus, it is generally accepted that blood total and LDL-cholesterol levels are major risk factors for CHD, and that dietary factors affecting blood cholesterol levels affect the risk of CHD (Refs. 20, 31, and 33 through 35).

FDA has limited this review to those aspects of the dietary lipid and cardiovascular disease relationship for which the strongest scientific evidence and agreement already exists. This limitation was necessary because of the extremely large volume of literature available on the broader topic. Even with the narrow focus on dietary intakes of saturated fat and cholesterol, blood cholesterol levels, and risk of CHD, the volume of available scientific literature was large. Moreover, the focus that FDA has chosen is most consistent with current dietary guidelines for the U.S. population.

C. Regulatory History

1. Fat, Fatty Acids, and Cholesterol Labeling

The regulatory history of nutrient content and descriptive labeling for fat and related lipids reflects the changing nature of the scientific evidence over the years and also the increasing acceptance of research results by the general scientific community. Early emphasis was on dietary cholesterol. Later, as more research results became available, saturated fats were recognized as the primary dietary factor related to elevated blood cholesterol and to risk of CHD. At one time, it was felt that dietary modifications should be undertaken only under a physician's care. More recently, dietary recommendations for the general population have become the norm.

A detailed history of FDA policies on labeling of fat, fatty acids, and cholesterol is provided elsewhere in this issue of the **Federal Register** in the document on the use of nutrient content claims for these nutrients. Because of the availability of that history, FDA believes that it is not necessary to repeat it in detail here.

2. Health Claims

For many years, FDA has permitted firms to label foods with truthful, nonmisleading information about nutrient content. In the past, however, the agency did not permit firms to provide consumers with information in the label or labeling concerning how the food may be used to affect a disease or health-related condition because such claims could make the food a drug. A complete description of FDA's regulatory history in the area of health messages (subsequently, in this proposal, the term "health claim" is used in place of "health message" for consistency with terminology used in the 1990 amendments) is published elsewhere in this issue of the **Federal Register**, § 101.14. A brief summary is presented here.

In the **Federal Register** of March 14, 1973 (38 FR 6951), FDA promulgated regulations that provided, in part, that a food shall be deemed to be misbranded if its labeling represents, suggests, or

implies that the food, because of the presence or absence of certain dietary properties, is adequate or effective in the prevention, cure, mitigation, or treatment of any disease or symptom (see current 21 CFR 101.9(i) (1)).

In the **Federal Register** of August 4, 1987 (52 FR 28343), FDA proposed to change its policy to permit the appropriate use on food labeling of health claims. That document proposed to amend nutrition labeling regulations in § 101.9 to permit health claims when (1) they are truthful and not misleading; (2) they are supported by valid, reliable, and publicly available scientific evidence derived from well-designed and conducted studies consistent with generally accepted scientific procedures and principles performed and evaluated by persons qualified by expertise and training in the appropriate disciplines; (3) they are consistent with generally recognized medical and nutritional principles for a sound total dietary pattern; and (4) the food bears nutrition information in accordance with the requirements of § 101.9. There were wide differences in opinion and numerous adverse comments were received in response to the proposal.

In the **Federal Register** of August 8, 1989 (54 FR 32610), FDA published a request for comments on a wide range of food labeling issues, including health claims. On December 7, 1989, FDA convened a public hearing in Seattle. The topic of health claims was the prime focus.

Based on comments received, FDA withdrew the August 1987 proposal and published a reproposal in the **Federal Register** of February 13, 1990 (55 FR 5176). The 1990 reproposal proposed to more narrowly define appropriate health claims. As part of this reproposal, the agency stated that six topic areas would be evaluated for their appropriateness for health claims including lipids and cardiovascular disease.

D. Evidence Considered in Reaching the Decision

The agency has reviewed all relevant scientific evidence on saturated fat and cholesterol and their relationships to blood cholesterol levels (specifically total cholesterol and LDL-cholesterol) and risk of CHD. The scientific evidence reviewed included all conclusions reached in: "The Surgeon General's Report on Nutrition and Health" (Ref. 35); "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 29); "The Lipid Research Clinics Population Studies Data Book," Volume II, "The Prevalence Study—Nutrient Intake," (Ref. 149); "Population Strategies for Blood Cholesterol Reduction" (Ref. 33); "High Blood Cholesterol in Adults, Detection, Evaluation, and Treatment" (Ref. 31); "Hypertension and High Blood Cholesterol, Working Report on Management of Patients With" (Ref. 32); "The Relationship Between Dietary Cholesterol and Blood Cholesterol and Human Health and Nutrition" (Ref. 150); "Nutrition Monitoring in the United States, an Update Report on Nutrition Monitoring" (Ref. 30); and "Healthy People 2000: National Health Promotion and Disease Prevention Objectives" (Ref. 36).

The agency also considered the reports of recognized non-U.S. Government scientific bodies that bear on this topic. FDA reviewed the National Research Council's (NRC's) "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 20); "Recommended Dietary Allowances" (Ref. 136); "Lipids and Cardiovascular Disease" (Ref. 78); and "Diet, Nutrition, and the Prevention of Chronic Diseases" (Ref. 151).

To ensure that its review of the scientific evidence was complete, in the **Federal Register** of March 28, 1991, FDA published a notice (56 FR 12932) requesting scientific data and information relevant to the 10 specific topic areas identified in section 3(b)(1)(A) of the 1990 amendments, including dietary lipids and cardiovascular disease.

The agency reviewed and considered all comments submitted in response to the **Federal Register** notice in developing this document. Furthermore, the agency updated the conclusions reached in these documents by reviewing all human studies that have appeared in the literature since the publication of the documents listed above and all review articles. The agency also considered the results of nonhuman primate studies to the extent that they clarified human studies or suggested possible mechanisms of action.

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

In response, to the FDA's request (56 FR 12932), FDA received 23 comments from food manufacturers, nutrient or dietary supplement manufacturers, national organizations of nutritionists and public health professionals, trade associations of nutrient supplement manufacturers, private physicians and health foundations, faculty of medical schools, and the Government of Canada. The comments dealt with the issue of lipids and cardiovascular disease as well as with the provisions and requirements of the 1990 amendments in general. FDA reviewed all of the documents, including books, abstracts, review articles, and scientific articles that were submitted. When appropriate, FDA included data submitted in scientific articles or books in its scientific literature review.

The majority of the comments, with one exception, expressed the view that the link between dietary fat and cholesterol intake and risk for cardiovascular disease was very strong. Many comments raised issues concerning the safety of polyunsaturated fatty acids in foods and supplements. Comments suggested that safety issues related to polyunsaturated fatty acids included increased risk of cancer and coronary thrombosis in humans, effects on immune function, and a role in osteoporosis. Comments recommended that consumption of foods (i.e., those high in salt) that alter other risk factors for CHD (i.e., hypertension) be included in the risk factor assessment of CHD.

The Director General, Food Directorate, Health and Welfare, of Canada submitted information on the regulatory status of health claims in that country which it considered helpful in the context of increased harmonization of regulations or standards affecting trade in specific products. Canadian law prohibits health claims on labels or in advertising when a nutrient is described for treatment, prevention, or cure of 46 diseases and disorders, including heart disease. On the relationship of the nutrient to the disease, the Canadian document stated:

> * * * the evidence linking saturated fatty acid intake with elevated blood cholesterol and the risk of heart disease is among the most persuasive of all diet-disease relationships. * * * Dietary cholesterol, though not as influential in affecting levels of blood cholesterol, is not without importance.

The Director General also stated that food label health claims regarding the role of fats in CHD risk would likely result in a food product being classified as a drug because the Food and Drug Act in Canada prohibits the advertising and sale to the general public of a food that is represented either by label or in advertising as a treatment, preventative, or cure for some 46 diseases, disorders, or abnormal physical states. Heart disease is among the major diseases for which such claims are prohibited.

Comments from national organizations of nutritionists and public health professionals advised that the agency should take a cautious approach to the use of health claims on foods and supplements with particular attention to avenues by which such claims might be abused or misinterpreted by the general

public. The comments recommended that scientific agreement should be the cornerstone for the use of health claims and that FDA should consider the data submitted in the context of meeting dietary requirements through intake of food. The comments asserted that only about 25 percent of the population may be responsive to reduction in dietary cholesterol and saturated fat, and thus the majority of the population at risk of cardiovascular disease may require medical advice and guidance and may need medication or a combination of medication and diet to achieve satisfactory lowering of serum cholesterol.

One comment recommended use of a formula that would indicate the cholesterol and saturated fat concentration in food. The term "cholesterol-saturated fat index" (CSI) was suggested. A low CSI index would indicate a low saturated fatty acid and cholesterol content. The use of such an index in planning low fat diets or in identifying potentially atherogenic foods was suggested. Comments from food manufacturers identified a number of modifiable risk factors for cardiovascular disease including dietary intake of saturated fat and cholesterol, sodium, fiber, and antioxidant vitamins. The manufacturers noted that both lifestyle and diet can have significant impacts on the risk of cardiovascular disease. One manufacturer submitted model health claims and examples of labeling. Another manufacturer suggested that the agency identify threshold levels of fats (saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, total fat), and threshold levels of other dietary nutrients in relationship to fats. The comments expressed concern that deficiencies might be produced by significantly decreased fat intake. A manufacturer noted that a low fat food should contain the usual levels of all other important nutrients commonly found in that food. A manufacturer commented that low fat foods containing high concentrations of salt and sugar may lead to increased risk of cardiovascular disease by increasing hypertension and obesity, respectively.

One manufacturer expressed concern about varying nutrient densities of foods and how best to express nutrient content of foods. One food manufacturer suggested a need for further research in the area of trans fatty acids and serum cholesterol levels.

An association of medical professionals provided a number of references that suggest serum cholesterol goals for patients with noninsulin-dependent diabetes mellitus and patients with hyperlipidemia.

Trade organizations of supplement manufacturers provided a number of comments on the value and safety of dietary supplements and suggested categories under which health claims on dietary supplements might be classified. Comments also expressed concern about the amount of saturated fatty acids and total fat contained in the 2,350 calories per day reference diet proposed by FDA as the basis for nutrition labeling for the general food supply. The comments stated that this level of calories may represent excess calories, saturated fat, and total fat for a significant proportion of the population (i.e., women).

Comments from professional medical associations and members of university medical faculties suggested that the emphasis of health claims regarding fat and cardiovascular disease should be on reduction of both saturated fatty acids and total fat, and that complex carbohydrates are recommended as the major replacement for calories from fat.

Comments were submitted regarding definitions for saturated fatty acids and polyunsaturated fatty acids. One comment suggested that saturated fatty acids be subdivided in a manner analogous to the subdivision of omega-3 and omega-6 polyunsaturated fatty acids. The comment noted that fatty acids of less than 12 carbons in length (for example, lauric acid) are metabolized by the liver, while saturated fatty acids of more than 12 carbons in length are metabolized through the lymphatic system.

One comment dealt with the Keys equation (Ref. 20) and noted that the equation does not have a term for the amount of monounsaturated fatty acids.

As appropriate, comments will be responded to in this document in the review of the scientific literature or in the discussion of the proposed regulation.

II. Review of the Scientific Evidence

A. Federal Government Documents

In 1982, a monograph derived from the population studies of the Lipid Research Clinics Program (Ref. 149) provided extensive information on the prevalence of hyperlipidemia (elevated blood lipids) in the United States. The data from 17 Lipid Research Clinics throughout the United States were derived from a series of epidemiologic surveys aimed at identifying the distribution, causes, and consequences of hyperlipoproteinemia (elevated levels of lipid transport particles in the blood).

A report to Congress pursuant to the Food Security Act of 1985 (Ref. 150) prepared by the Department of Health and Human Services and U.S. Department of Agriculture (DHHS/USDA) concluded that carefully controlled studies under metabolic ward conditions leave little doubt that increasing dietary cholesterol will induce a rise in plasma total cholesterol in most people. The report stated that when all data are taken together, the increase in plasma cholesterol resulting from ingestion of dietary cholesterol averages about 10 mg cholesterol per 100 milliliters (decaliters (dL)) for every 100 mg dietary cholesterol per 1,000 calories consumed. Thus, the report stated, increasing dietary cholesterol from 300 to 500 mg per day for a person consuming 2,000 calories per day will cause an increase in the plasma cholesterol of about 10 mg per dL. The report found that the major effect of dietary cholesterol is to raise the LDL-cholesterol fraction of total blood cholesterol.

Comprehensive reviews of the relationship of dietary fats and CHD are included in recent Federal government reports. In 1988, the "Surgeon General's Report on Nutrition and Health" (Ref. 35) reviewed studies of associations between dietary factors and risk of chronic disease. The Surgeon General's report found that results of epidemiologic, clinical, and animal studies provided strong and consistent evidence for a relationship between high intakes of saturated fat, high blood cholesterol, and increased risk of CHD. Conversely, reductions in blood cholesterol levels reduce the risk of death from CHD. The report noted that excessive dietary saturated fat is the major contributor to total blood cholesterol levels. The report also noted: (1) The effect of dietary cholesterol on blood cholesterol levels is less consistent than that for saturated fats (Ref. 35); (2) the roles of other dietary fats such as monounsaturated fatty acids and polyunsaturated fatty acids were not well defined. The Surgeon General's report concluded that the disproportionate consumption of foods high in fats was of primary concern for Americans. The Surgeon General's report recommended reduction in intake of fats (especially saturated fats and cholesterol). Although the relationship of CHD and lipids was primarily attributable to saturated fats and cholesterol, the recommendation for changes in American dietary patterns included a reduction in consumption of total fat because of the possible association of total fat with risk of other

diseases (cancer and diabetes), because of the likely role of high dietary fat intakes in increased risk of obesity (another risk factor for CHD), and because a decrease in total fat consumption facilitates a reduction in saturated fatty acids.

DHHS and USDA in "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 29) state that the lipids in American diets most often and most strongly associated with increased risk of atherosclerotic CHD are saturated fat and cholesterol. CHD rates and population risk were most strongly related to average serum cholesterol levels, particularly LDL-cholesterol levels. According to this report, other factors strongly linked with increased risk of CHD are high blood pressure, smoking, and diabetes. The relationship between obesity and CHD risk was more variable. Among the recommendations from the DHHS/USDA report to Congress relating to decreasing the risk of CHD include: decreasing the total amount of fat in the diet to less than 30 percent of calories; decreasing the amount of saturated fat in the diet to less than 10 percent of calories; eating less animal fat (the source of all dietary cholesterol) to aid in reducing serum cholesterol; and restricting intake of salt to aid in decreasing blood pressure (Ref. 150).

Reports from the National Cholesterol Education Program (NCEP); National Heart, Lung, and Blood Institute, National Institutes of Health, 1988 to 1990) reached similar conclusions regarding relationships among intake of dietary saturated fats and cholesterol, elevated blood cholesterol levels, and CHD (Refs. 31 through 34). The reports noted that approximately 55 percent of adult Americans have cholesterol levels at or above a desirable level. The reports also emphasize the important roles of genetic and environmental factors in blood cholesterol levels. The reports concluded that excessive intake of saturated fat, total fat and dietary cholesterol, together with excessive body weight, all contribute to elevated blood cholesterol levels. The reports stated that the role of total fat intake is not direct, but reduced fat intake aids in decreasing intakes of saturated fat and cholesterol and may facilitate maintenance of ideal healthy body weight. The National Cholesterol Education Program (NCEP) (Refs. 31, 33, and 34) recommended the following pattern of nutrient intake for healthy Americans:

(1) Consume less than 10 percent of total calories from saturated fatty acids;

(2) Consume an average 30 percent of total calories or less from all fat;

(3) Consume dietary energy in amounts needed to reach or maintain a desirable body weight; and

(4) Consume less than 300 mg of cholesterol per day.

The NCEP panel, noted compelling evidence that the atherosclerotic process (and hypertension) begins in childhood and progresses into adulthood. Toddlers over 2 years of age may safely make the transition to recommended eating patterns as they begin to eat with the family (Ref. 34). The NCEP recommendations are not intended for infants from birth to 2 years of age (Ref. 34).

The Public Health Services (PHS) DHHS report "Healthy People 2000: National Health Promotion and Disease Prevention Objectives," (Ref. 36) noted that cardiovascular disease, primarily CHD and stroke, kill nearly as many Americans as all other diseases combined, and that a casual relationship between high blood cholesterol and CHD has been demonstrated (Ref. 36). As noted in other Federal government documents, the report stated that the key modifiable factors that influence risk of CHD include: cigarette smoking, high blood cholesterol, high blood pressure, excessive body weight, and sedentary lifestyle. Reducing death from heart disease and stroke, and reducing mean serum cholesterol level among adults to no more than 200 mg per dL, are among the major public health goals identified in the Healthy People 2000, report. The Healthy People 2000 report recommended that Americans should reduce dietary fat intake to an average of 30 percent of calories or less and average saturated fat intake to less than 10 percent of calories in order to help achieve these goals.

B. Reviews From Recognized Scientific Bodies

The National Research Council's 1989 report, "*Diet and Health:* Implications for Reducing Chronic Disease Risk" (Ref. 20) reviewed the role of dietary fats and risk of chronic disease. The report concluded that there is clear evidence that the total amount and types of fats and other lipids in the diet influence the risk of cardiovascular disease (Ref. 20), and that evidence that intake of saturated fatty acids and cholesterol are causally related to CHD (CHD) is especially strong and convincing. The report recommended that persons in the general population limit their intake of total fat to 30 percent of calories and reduce their intake of saturated fatty acids to 10 percent or less of total calories. The report stated that individual responses to dietary cholesterol vary, but noted that, on average, intakes exceeding 100 mg of dietary cholesterol per 1,000 calories elevates LDL-cholesterol by 8 to 10 mg per dL. They recommended limiting dietary cholesterol intake to 300 mg per day or less.

LSRO/Federation of American Societies for Experimental Biology (FASEB) (Ref. 78) prepared an evaluation of the scientific literature on the relationships between dietary lipids and cardiovascular disease, particularly CHD (Ref. 78). The LSRO's conclusions support the major conclusions of the Federal government and other reports from recognized scientific bodies on the role of dietary lipids (saturated fats, other fats, and cholesterol) in the risk of CHD.

With respect to cholesterol, the LSRO report concluded that: (1) Dietary cholesterol may be a greater dietary risk factor than generally realized; (2) almost all individuals respond to dietary cholesterol with at least some rise in serum cholesterol; (3) the danger of high dietary intakes of cholesterol for certain individuals who are high responders to dietary cholesterol may be even greater than the average; and (4) the average increase in serum cholesterol ranges from 6 to 10 mg per dL for each 100 mg cholesterol consumed per 1,000 calories. More recent analysis of epidemiologic data suggests that an increase of 1 mg serum cholesterol per dL, sustained for many years, increases risk of CHD by 1.5 percent. LSRO (Ref. 78) concluded that a strong case, based on circumstantial evidence, implicates dietary cholesterol in atherogenesis, and therefore supports current dietary recommendations to limit dietary cholesterol consumption to less than 300 mg per day.

C. Review of the Scientific Literature

1. Background

CHD is the most common and most serious form of cardiovascular disease. Atherosclerosis is the underlying pathogenic cause in the development of CHD. A relationship between dietary lipids, deposition of cholesterol esters in arterial walls, and CHD was hypothesized early in this century (Ref. 20). Animal studies provided the first direct evidence linking diets high in saturated fat and cholesterol to cholesterol accumulation in atherosclerotic lesions. In this document, the agency reviews pertinent studies relating high intakes of dietary lipids (particularly saturated fats and cholesterol) to elevated serum cholesterol levels and to risk of CHD.

2. Criteria

The criteria used to select pertinent studies required them to be publicly available in English, to present primary data, to include direct measurements or quantitative estimates of dietary lipids, and to include measurements of risk of CHD (incidence and prevalence rates, mortality, or clinical measures of blood total or LDL-cholesterol levels).

In the agency's evaluation of the scientific literature on the relationship of dietary lipids (saturated fat and cholesterol), blood cholesterol levels, and risk of CHD, FDA gave more weight to human studies than to studies in animal models. Because the conclusions of the Federal government and other review documents most consistently identified saturated fat and cholesterol as causally related to CHD risk, a review of studies on other than nonhuman primates and on aspects of cardiovascular disease other than CHD published subsequent to the most recent Federal government reviews, and other reviews by recognized scientific bodies, was not included in this review. Similarly, study results for end points other than CHD or the clinical intermediates of blood total and LDL-cholesterol were also not reviewed due to time constraints and because of the strong focus on these measures in the reports of government and others.

FDA reviewed several types of epidemiologic studies. The strengths and weaknesses of different types of epidemiologic studies and the methodologies for assessment of dietary intakes are reviewed elsewhere (Ref. 20).

FDA generally gave the greatest weight to randomized, double-blind, controlled (placebo or self) clinical trials. Dietary intervention studies conducted for shorter periods of time with fewer subjects were used to support conclusions of large clinical trials. FDA looked for repeated and consistent findings across different types of studies and different population groups. Data were evaluated against general criteria for good experimental design, execution, and analysis. FDA evaluated the weaknesses and strengths of individual studies; then looked at the strength of the overall combined evidence, taking into account the strength of the association, the consistency of findings, specificity of the association, biological plausibility, and dose response. Because of general scientific agreement prior to this review, FDA also looked for consistency or inconsistency with prior conclusions.

The relationships among dietary fats, including saturated fats, cholesterol, and risk of CHD are complex. For this reason, common measures or elements of diet and assessment of risk of CHD were sought in all studies. These measures or elements include the following:

(a) Identification of level of dietary lipids most consistently related to raising levels of blood cholesterol. As a minimum, information on intakes of saturated fat and cholesterol was required;

(b) Identification of commonly used clinical measurements in the assessment of development or progression or risk of CHD. As a minimum, studies were required to have measurements of total cholesterol. Measurements of low density lipoprotein cholesterol (LDL-cholesterol) were deemed desirable;

(c) Observation of clinically manifest CHD including, for example, myocardial infarction, angiographically demonstrated lesions, CHD mortality, and total mortality, were deemed desirable when measures of blood cholesterol were available. These measures were essential in the absence of blood cholesterol data.

3. Dietary Lipids and Risk of CHD

a. *Epidemiologic studies*—i. *Background.* Epidemiologic studies describing the relationship between dietary fats, their effect on blood cholesterol levels, and risk of CHD were described and reviewed extensively in Federal government reports (Refs. 33, 35, and 36), other documents (Ref. 20), and in many reviews cited in these documents. The Federal government and other reviews by recognized scientific bodies concluded that there was strong and consistent evidence that blood total cholesterol and LDL-cholesterol levels are a cause of CHD (Refs. 20, 31, 33, and 36); they estimated that on average, a 1 percent reduction in serum cholesterol is associated with a 1.5 to 2 percent reduction in risk of CHD (Refs. 20, 31, 33, 63, 79, 80, and 147).

FDA reviewed a number of studies and reviews (including meta-analysis of epidemiological and clinical trials) published subsequent to 1987 (Refs. 1, 17, 27, 62, 63, 74, 75, 77, 80, 98, 108, 109, 112, 113, 114, 117, 120, 128, 129, 130, 132, 137, 141, 147) on the relationship of blood cholesterol and CHD and confirmed that more recent studies confirmed and strengthened the previous conclusion.

This section (II. D.) begins with a brief description of two epidemiologic studies reviewed by the Federal government and other reviews by recognized scientific bodies (Refs. 20 and 35) and which describe the relationships between dietary lipids (saturated fat, total fat, and cholesterol) and blood cholesterol levels. The design, results, and conclusions of epidemiologic studies subsequent to the above conclusions are contained in Table 1 of this document.

In the seven countries study, which was conducted in the United States and six other countries, and included 11,579 men 45 to 49 years of age, 7-day food records and duplicate meals were collected and analyzed to determine the relationship of intake of specific dietary lipids to serum cholesterol (Ref. 35). The results demonstrated a positive correlation between calories consumed from total fat and serum cholesterol levels ($r=0.67$). Correlations between intake of saturated fat and dietary cholesterol and between dietary cholesterol and serum cholesterol were stronger (0.87 and 0.90, respectively). The results of the study showed that there were substantial variations in the amounts and types of fats consumed by different populations. Average blood cholesterol levels and rates of CHD were highly correlated with the percent of calories derived from saturated fatty acids and less strongly correlated with total dietary fat intake. Furthermore, the study provided strong evidence that the risk of CHD is continuous across a wide range of serum cholesterol levels (Ref. 20). The NCEP Expert Panel (Refs. 31 and 33) concluded that this study provided strong epidemiologic support for the relationship between diets high in saturated fat and increased risk of CHD.

The Ireland-Boston Diet-Heart Study (Refs. 20, 35, and 73) was a prospective study of middle-aged Irish men residing in Ireland and brothers who had migrated to Boston. Each group consumed diets typical of their places of residence. Brothers living in Ireland or in Boston who consumed low-fat, low cholesterol diets had similar age-adjusted serum cholesterol levels. The Irish immigrants who adopted the high-fat diet of Boston (16 to 18 percent of calories as saturated fat; 2 to 3 percent of calories as polyunsaturated fat; and 233 to 273 mg cholesterol per 1000 calories) had higher serum cholesterol levels and higher risk of CHD than brothers consuming diets lower in fat and cholesterol. Thus, a positive association was found between dietary intakes of saturated fat and cholesterol and elevated serum cholesterol and risk of CHD among men with similar genetic backgrounds but whose dietary patterns and lifestyles differed.

Based on these and similar results from numerous other studies the Federal government and other reviews

concluded that an extensive amount of evidence (derived from a variety of types of epidemiologic studies and reinforced by other kinds of research) demonstrated that dietary lipids, particularly saturated fat and cholesterol, are highly correlated with blood cholesterol and rates of CHD (Refs. 17, 27, 103, 109, and 131). Current intake of saturated fat in the U.S. American diet has been estimated to average about 13 percent to 14 percent of total calories (Refs. 20 and 29).

ii. *Update.* FDA reviewed all human studies subsequent to 1987 to determine whether conclusions reached in the Federal government and other reviews by recognized scientific bodies needed to be modified based on the results of more recent findings. In the short review below, studies dealing with omega-3-fatty acids are not considered because the relationship of omega-3-fatty acids and heart disease is the subject of another health claims proposal published elsewhere in this issue of the **Federal Register.** For reasons discussed previously, reporting of results is limited to dietary intakes of saturated fat and cholesterol relative to blood total cholesterol, LDL-cholesterol, or risk or occurrence of CHD.

In a cross-sectional analysis of 976 African men and women of color aged 15 to 64 years, there was a significant independent correlation between blood total cholesterol and dietary intakes of specific types of fat and cholesterol (Ref. 134). Consumption of diets high in fat and saturated fat (37 and 12.3 percent of calories, respectively) and cholesterol (greater than 310 mg per day) were positively correlated with increased blood cholesterol levels (7.5 millimole (mmol) per l or 290 mg per dL) compared to 4.5 mmol per l (174 mg per dL) in the group that consumed less fat (35.8 percent), saturated fat (10.8 percent) and cholesterol (284 mg per day) (Ref. 134).

The relationship between composition of foods and CHD risk factors, including serum cholesterol, was analyzed in the study by Trevisan et al. (Ref. 139). This cross-sectional study of 10,800 middle-aged men and women in 9 Italian communities (dietary data obtained by questionnaire) showed that higher serum cholesterol levels (5.65 mmol/L; 218 mg/dL) (5.65 mmal/L; 218 mg/dL) were strongly associated with diets high in butter (relatively high in saturated fat and low in other types of fatty acids) (Ref. 139). Additionally, lower levels of blood cholesterol (5.45 mmal/L; 210 mg/dL) were associated with dietary patterns characterized by higher intakes of olive oil and vegetable oil (relatively low in saturated fat and high in polyunsaturated fat and monounsaturated fat) (Ref. 139).

A Belgian study of 5,485 men and 5,456 women showed that in both sexes, higher saturated fat (17.3 percent of calories) and dietary cholesterol (435 mg/day) intakes were associated with higher total cholesterol levels (235 mg per dL) after adjustments were made for lifestyle and physiologic variables using multiple regression-analysis (Ref. 68). Lowik et al. (Ref. 83) studied 199 elderly men and 180 elderly women (65 to 79 years of age) and found a positive correlation between intake of saturated fat (assessed by dietary history) and blood total cholesterol in women but not in men.

Dietary and cross-checked lifestyle questionnaires were used to determine the relationship of diet to serum lipids in 315 free-living Dutch males between 28 and 29 years of age (Ref. 5). The typical Dutch diet contained 39 percent fat, 43 percent carbohydrate and 3282 calories per day. Consumption of a diet high in saturated fat (15.5 percent of calories) and cholesterol (128 mg per 1,000 calories) showed a weak but significant positive association with total serum cholesterol and LDL-cholesterol. Many other epidemiological studies are described in Table 1 which relate diet intakes of dietary fat, especially fatty acid and to blood cholesterol levels (Refs. 28, 40, 51, 70, 83, and 143).

Results of a reanalysis of data collected in the Israeli survey of 8,829 men (40 to 60 years of age) showed a highly significant positive relationship between intake of dietary saturated fat and elevated serum cholesterol. Data were adjusted for intra-individual variability by use of a regression model (Ref. 70).

A prospective study in Japan involving two cohorts of men and women with greater than 2,250 subjects in each cohort monitored dietary animal fat intake and serum cholesterol levels for 7 to 11 years (Ref. 121). At baseline, each cohort was 40 to 69 years of age in 1963 to 1966 or in 1972 to 1975. At initiation of the study, animal fat intake (as determined by random food collection, interviews, and 24-hour dietary recalls) was 4.5 percent of daily calories in the 1963 to 1965 cohort and 9.6 percent of daily calories in the 1972 to 1975 cohort. Serum cholesterol increased 22 mg/dL in men and 29 mg/dL in women which was highly correlated with high intakes of animal fat in every age group and for both genders, but there was no significant change in CHD during the two decades. Serum cholesterol was inversely associated with cerebral hemorrhage in the early cohort.

FDA reviewed meta-analyses and primary data from epidemiologic and clinical studies which analyzed the relationship of lowering of serum cholesterol to risk of CHD (Refs. 12, 14, 16, 17, 42, 63, 76, 85, 86, 100, 130, 137, 141, 146, and 147). Meta-analysis combines data collected with differing methodologies. This complicates data analysis and assessment.

Bush et al. (Ref. 17), in a meta-analysis of nine prospective studies, found that in women a diet low in saturated fat and cholesterol was associated with lower levels of blood total cholesterol and LDL-cholesterol (Ref. 17). Women with total blood cholesterol values greater than 265 mg per dL were at three times greater risk of CHD than women with blood cholesterol below 220 mg per dL.

Shekelle and Stamler (Refs. 120 and 130) reviewed and reanalyzed published epidemiologic studies to evaluate the strength of the effect of dietary cholesterol intakes on serum cholesterol and risk of CHD. The authors evaluated whether dietary cholesterol alone had an independent effect on blood cholesterol. They evaluated four prospective studies (Western Electric study, Ireland Boston Diet-Heart Study, the Zutphen study, and the Honolulu Heart Program) published since 1981. Dietary cholesterol intake in individuals was found to be significantly and positively related to their long-term risk of CHD, independent of, and in addition to, serum cholesterol, blood pressure, and tobacco use. On average, a dietary intake of 300 mg cholesterol per 1,000 calories was associated with a blood cholesterol that was increased approximately 6 to 7 percent. On average, a 200 mg per 1,000 calorie higher intake of cholesterol at baseline was associated with a 30 percent higher CHD rate (95 percent confidence interval).

In summary, recent epidemiological studies evaluated the relationships of dietary fat intakes and blood cholesterol levels. In general, these studies reported significant independent positive correlations between serum total cholesterol and dietary intakes of saturated fat and cholesterol.

There are several detailed recent reviews of this area (Refs. 48, 62, 63, 74, 75, 117, 129, 130, 148). These reports also concluded that there was substantial epidemiologic evidence showing that consumption of dietary fats, especially saturated fatty acids and cholesterol, was highly positively correlated with elevated blood cholesterol and risk of CHD.

b. *Clinical studies*—i. *Background.* Even in very large epidemiologic studies, it is difficult to identify a relationship between dietary intake of a specific nutrient and a disease. One problem is that diets consumed by study participants are not homogeneous, and it is difficult to accurately quantify dietary intakes from dietary recall records. Clinical studies, however, are able to estimate the effects of particular foods or food components with respect to a specific disease process. Clinical trials provide more specific, definitive, and quantitative information on the relationship of dietary components (for example, saturated fat or cholesterol) and to risk factors related to CHD (for example, levels of serum cholesterol).

Federal government reports and other reviews by recognized scientific bodies described and extensively reviewed a wide variety of clinical trials and concluded that the results of clinical trials support epidemiologic studies and show that diets high in saturated fat and cholesterol are strongly correlated with high levels of serum cholesterol (Refs. 20, 31, 33, and 35). These reports also note that some research has also been directed toward identification of specific fatty acids which alter serum cholesterol levels. For example, saturated fatty acids, such as palmitic (C–16), myristic (C–14), and lauric acid (C–12), are more cholesterol-raising than other saturated fatty acids (Ref. 20). However, the reports varied considerably in the emphasis placed on these findings and none of the reviews specifically targeted these three saturated fatty acids when making recommendation for dietary changes by the U.S. population.

The Federal government and other reviews concluded that possible roles of other fatty acids (i.e., monounsaturated fats, polyunsaturated fats) modulating blood cholesterol levels and or CHD risk have been suggested by human studies, but that the evidence is weaker than those roles described for saturated fats and dietary cholesterol.

ii. *Update*—(1) *Dietary intervention to reduce serum.* Dietary intervention trials are reviewed in Table II. The effect of a low fat, low cholesterol diet on serum cholesterol levels, myocardial infarction, and mortality from CHD was assessed in the Minnesota Coronary Survey, a double blind, randomized, open enrollment, dietary trial that included 4,393 men and 4,664 women. The study was conducted in six state mental hospitals and one nursing home (Ref. 42). The patients consumed institution-provided diets for an average of 384 days. Two diets containing 39 percent of total calories as fat were compared. The control diet (a high saturated fat diet) provided 18 percent saturated fat, 5 percent polyunsaturated fat, 16 percent monounsaturated fat, and 446 mg cholesterol per day. The experimental diet (a low saturated fat diet) had less saturated fat (9 percent) and cholesterol (166 mg) and more polyunsaturated fat (15 percent) than did the control diet. Consumption of the low saturated fat diet was associated with a reduction in serum total cholesterol from 207 mg per dL to 175 mg per dL. Serum cholesterol levels in the control group remained at 203 mg per dL. Four and one-half years after starting the diet, however, no differences were observed in the population studied in myocardial infarctions, deaths from CHD, or total mortality. Eighty-one percent of the patients stayed in the hospital less than 1 year. There was, however, a decrease in numbers of deaths and myocardial infarctions in men and women in the 45 to 55 year old subgroup who consumed low saturated fat diets for more than 2 years. A similar change was not observed in the 35 to 39 year old group.

Women, as previously reported in men, with the highest basal serum cholesterol levels achieve the greatest reductions in serum cholesterol upon dietary intervention. In a recent study by Boyd et al. (Ref. 9) of 206 women over 30 years old with monographic dysplasia (breast cancer), half were placed on a low fat (total fat 21 percent, saturated fat 7 percent of total calories, respectively; cholesterol 244 mg per day), high carbohydrate (52 percent of calories) diet for 1 year. Total fat and saturated fat was 37 and 14 percent of total calories, respectively, and cholesterol 344 mg per day in the control diet. In women who consumed the low saturated fat diet, total serum cholesterol levels were significantly reduced by 8 percent at 4 months and serum cholesterol was most effectively reduced in women with the highest basal serum cholesterol levels. No significant changes in serum cholesterol were observed in the control group. The group that received dietary counseling had a significant decrease in body weight and low density lipoprotein cholesterol as well, which was not observed in the group that did not receive counseling.

The effectiveness of dietary instruction on the control of serum cholesterol levels was related in the following study. Curzio (Ref. 26) demonstrated that low fat, low saturated fat, and low cholesterol dietary counseling by trained dietitians' changes in dietary patterns are effective means of reducing serum cholesterol and risk of CHD. Half of 124 hypercholesterolemic and hypertensive patients received dietary counseling regarding low-fat, low-cholesterol diets and half did not (Ref. 26). At baseline the average serum cholesterol for all subjects was 6.5 mmol per 1 (250 mg per dL). Serum total cholesterol, measured two years later, significantly decreased in both groups compared to initial serum cholesterol levels. The group that received dietary counseling had a greater decrease in body weight, total cholesterol (12 percent compared to 8 percent in the control group), and LDL-cholesterol than did the group which did not receive counseling.

(2) *Multifactorial clinical intervention.* The corner stone of multifactorial clinical intervention for reduction in serum cholesterol is low saturated fat and low cholesterol diets as a part of larger lifestyle changes. These multifactorial clinical trials often include several concomitant changes including: the use of a combination of interventions diets low in fat, saturated fat, cholesterol, and sodium, control of high blood pressure, reduction in smoking; stress management; and moderate exercise programs. A 10.5 year followup of the Multiple Risk Factor Intervention Trial (MRFIT), which involved 12,866 men at risk of CHD was recently reported. Half (n=6,428) of the subjects were assigned to special intervention and the other half 6,438 to usual care. A significant decrease (24 percent) in mortality due to acute myocardial infarction and a 7.7 percent decrease in death from all causes (Ref. 101) was observed. This study demonstrates in subjects at risk of developing CHD that multifactorial dietary and lifestyle changes reduce risk. These data can also be cautiously applied to the general population who possess more than two risk factors for CHD.

A small multifactorial intervention trial (71 subjects, 55 who were at high risk of developing CHD) used a low fat-vegetarian diet (6.8 percent of calories) and reported significant regression of coronary lesions (Ref. 106). There was no regression of the disease in control subjects who consumed higher fat diet (29.5 percent of total calories.

(3) *Metabolic studies.* "Metabolic ward" studies are conducted under tightly controlled conditions. Such studies, however, due to their short duration (usually less than 2 months) and small numbers of subjects (usually less than 50 subjects) have less predictive value for determining risk of CHD than do clinical trials. Metabolic ward studies do provide important

information regarding possible specificity, dose-response relationships, short-term effects and possible mechanisms by which dietary fats and cholesterol affect serum cholesterol and risk of CHD. These studies allow for cautious conclusions to be made on the effects of dietary lipids on serum lipids and can be used to confirm inferences derived from clinical studies.

Review of the extensive number clinical trials and clinical trials and metabolic ward studies which have been reported since the publication of the reports by the Federal government and by recognized scientific bodies (Refs. 2, 4, 6, 9, 20, 26, 31, 33, 35, 36, 42 through 45, 53, 54, 57, 69, 82, 88, 89, 92 through 94, 103, 105, 144) are not discussed in detail in the text of this document. Major features and results of a number of these studies are included in Table II, however.

In summary, these studies generally have shown that dietary fat affects blood cholesterol levels in most individuals. Not all dietary fats affect blood cholesterol levels to the same degree or in the same direction. In the majority of studies, dietary intakes in which saturated fat and cholesterol were low relative to basal or control diet showed an association with lower blood cholesterol levels and CHD risk. The nature of most of the studies did not permit conclusions as to links between intakes of specific types of fat (specific saturated fatty acids, monounsaturated, and polyunsaturated fatty acids) and effects on serum cholesterol. Results are, however, consistent with earlier conclusions in the reports by the Federal government and other recognized scientific bodies that diets low in saturated fats are associated with lower total blood cholesterol and LDL-cholesterol.

(4) *Dietary cholesterol and serum cholesterol.* In addition to linking diets high in saturated fat to increases in serum cholesterol levels, the Federal government and other reviews by recognized scientific bodies also concluded that high intakes of dietary cholesterol are associated with higher blood cholesterol levels. Several recent studies have examined this association. Current American intake of dietary cholesterol is approximately 425 mg per day for men and lower for women and children.

Healthy (n=10), free-living, normolipidemic men (average age 27 years) participated in a blinded crossover study designed to determine the effects of dietary cholesterol and exercise on serum cholesterol levels. Subjects who consumed low-fat diets (30 percent of calories with a polyunsaturated to saturated fatty acid constant value of 1.5), exercised aerobically 25 minutes per day, and were supplemented with 600 mg per day of cholesterol for 4 weeks showed increases in LDL-cholesterol compared to subjects fed diets supplemented with 200 mg per day cholesterol (Ref. 66). Individual responses were highly variable but there were significant increases in LDL-cholesterol. Three out of 10 subjects showed an increase in LDL-cholesterol of greater than 2-percent and two showed increases in LDL-cholesterol between 10 and 25 percent.

In a dietary intervention study, 56 free-living subjects previously identified by the authors as "hypo"- or "hyper"-responders to dietary cholesterol were placed on low fat diets (total fat was 29 percent, and monounsaturated fat was 7.5 percent of total calories and polyunsaturated fat to saturated fat content was held constant at a ratio of 1.5). The subjects were challenged with increased dietary cholesterol levels (ranging from 90 to 410 mg cholesterol per day) in a cross-over design (Ref. 41). Those subjects who were responders to saturated fats (blood cholesterol increased more than 8 percent) also showed a small increase in serum total cholesterol and LDL-cholesterol when challenged with increased dietary cholesterol while on 29 percent fat diets Thus response to dietary cholesterol was not totally dependent on saturated fat intakes. Other dietary cholesterol studies (Ref. 93) are described in Table II.

Segal (Ref. 118), using data from epidemiological and clinical studies, estimated that if individuals reduced consumption of dietary cholesterol from 300 mg per 1000 calories per day to 150 mg of cholesterol per 1000 calories per day without making any dietary change in fat or in total calories, they would experience in a 7.6 mg per dL decrease in blood cholesterol.

In summary, the limited number of dietary cholesterol intervention studies published subsequent to the reports by the Federal government and other recognized scientific bodies show results consistent with those reports, i.e., that dietary cholesterol has an independent effect on serum cholesterol level.

(5) *Individual differences in response to dietary lipids.* The variability in individual responses to dietary lipids is well-recognized (Refs. 20 and 35). Connor (Ref. 21) and Gotto (Ref. 50) reviewed possible mechanisms that may explain variations in individual response to lipids. These authors postulated that each individual may have a threshold amount of saturated fat or cholesterol that when consumed, will increase serum lipid levels (i.e., LDL-cholesterol), and a ceiling amount beyond which further dietary consumption of foods that elevate blood cholesterol will have no effect. The average threshold amount for most people would be 100 mg of cholesterol per day. An average ceiling amount would be approximately 300 to 400 mg per day.

D. Safety Considerations

Reductions in dietary intakes of saturated fat and cholesterol would presumably result in higher intakes of other dietary components (monounsaturated and polyunsaturated fats, carbohydrates, and commercially generated fats) since calories lost from decreased intake of saturated fats must be "made up" by other components. Increased intakes of other types of fats is a possible result. Some of these fats are not metabolized in a manner analogous to common dietary fats and are not generally found in diets to a significant degree.

It is possible that the amount and type of fats available for consumption by the public may change. The agency in its review of the recent scientific literature and comments received by the agency, has identified several areas of possible concern regarding changing American dietary patterns.

1. Trans-Fatty Acids

One area of potential concern is the increasing availability for consumption of trans-fatty acids. Trans-fatty acids (generally isomers of cis monounsaturated fatty acids) are primarily constituents of commercially hydrogenated or hardened natural vegetable oils used in the formulation of margarine, shortenings, salad and cooking oils. Trans-fatty acids may also be found in some meat and dairy products since they are synthesized in the rumen of cattle. Hydrogenation of vegetable oils high in unsaturated fatty acids is used to make oils more palatable or to meet functional needs in food processing. It has been estimated that from 2 percent to 7 percent of beef fat and butterfat, and from 10 to 30 percent of margarine, shortenings and salad oils consist of trans-fatty acids. This is equivalent to approximately 6 percent of total fat consumed in the US or 8.1 g of trans-fatty acids per person per day (Refs. 20 and 65).

The reports of the Federal government and other recognized scientific bodies concluded that most of the evidence indicates that trans-fatty acids, in the quantities currently consumed in the

U.S. diet, do not adversely influence serum cholesterol concentration, and that when substituted for saturated fatty acids, the trans-fatty acids may be associated with a decrease in serum cholesterol (Ref. 20). Studies that examine the effects of trans-fatty acids on serum cholesterol levels are limited, however, and often report conflicting results and conclusions. In addition, there may be other effects unrelated to lipid and lipoprotein metabolism, that deserve careful attention and additional investigation.

LSRO prepared a report on health effects of dietary trans-fatty acids for the agency in 1985 (Ref. 77). In 1885, the estimated average trans-fatty acid content in the U.S. food supply was about 5.5 percent. This level of trans-fatty acids was consistent with that found in human adipose tissue. The data suggested an association rather than a casual relationship.

Studies with individuals fed diets of similar fatty acid composition, except for the replacement of cis isomer (i.e., oleic acid) with the trans isomer (i.e., elaidic acid) of partially hydrogenated vegetable oils, showed that the trans oils were no more cholesterolemic than were the cis isomers (Ref. 77). Similar studies in which elaidic and oleic acid were fed to different experimental groups were not definitive and differences between groups in elevation in serum cholesterol were not significant. Short term studies in animals showed that dietary elaidic acid or partially hydrogenated vegetable are cholesterolemic but not atherogenic (Ref. 77).

In one recent study, the gluteal adipose tissue fat biopsies were removed from 76 free living U.S. males, average age 46.8 years, and analyzed for cis and trans-fatty acids (Ref. 64). No strong correlation was found between concentrations of trans-fatty acids and 10 cardiovascular risk factors, including clinical lipid profiles. The total level of trans-fatty acids in adipose triglyceride was 4.14 percent or equivalent to the proportion consumed in the diet. One isomer 7c–16 carbons:1 double bond (small c represents cis isomer) which is formed from a fatty acid found in hydrogenated shortening (9c–18 carbons:1 double bond) was positively correlated with four risk factors: body mass index, total cholesterol, LDL-cholesterol and systolic blood pressure.

Recently Mensink (Ref. 95) conducted a randomized cross-over design study which included 34 women and 25 men to assess the effect of trans-fatty acids on serum lipids. The average age of the subjects was 25.5 years and all were healthy. The isocaloric diets fat (39 percent of calories, mean calories 2,700 differed in that 10 percent of the total energy was provided as either oleic acid (cis), elaidic acid (the trans form of oleic) or saturated fat (lauric and palmitic acid). Each diet was fed for 3 weeks. The trans-fatty acid diet (saturated fatty acid 10 percent of calories, plus 11 percent additional from trans-fatty acid) increased LDL-cholesterol by 14 mg per dL compared to the oleic acid diet. The diet high in saturated fat (19.4 percent of calories) increased LDL-cholesterol by 18 mg per dL compared to the oleic acid diet (saturated fat 9.5 percent of calories). Trans-fatty acid also produced a small, but significant increase in triglycerides compared to the oleic acid enriched diet. Since the trans-fatty acids increased LDL-cholesterol this could conceivably increase the risk of CHD. The concentration of trans-fatty acid used in the diet was higher than current U.S. consumption. More studies are needed to confirm these results, to determine dose response levels, and to identify populations most sensitive to trans-fatty acids. The issue of the biological effects of hydrogenation of polyunsaturated fatty acid vegetable oils is unresolved.

In its recent evaluation, LSRO concluded on the basis of several reports both prior to 1987 and one major study subsequent to 1987, that there is a strong possibility that trans-monounsaturated fatty acid (i.e., elaidic acid), may raise blood LDL-cholesterol and thus may have atherogenic potential (Ref. 78).

2. Other Safety Considerations

a. *Cholesterol gallstones.* The reports of the Federal government and other recognized scientific bodies conclude that being female and being obese are the factors most consistently associated with gallstones (accumulation of bile supersaturated with cholesterol) (Ref. 20)). There is conflicting and inconsistent evidence regarding a possible effect of diets high in polyunsaturated fats on gallstones (Ref. 20). There is no evidence that intakes of polyunsaturated fats up to 10 percent of total calories affect susceptibility to or induces gallstones in humans.

The relationship of diet and gallstones is reported in the update of the scientific literature. Chileans and some North American Indians commonly consume diets low in both total and saturated fat, but high in complex carbohydrates, and have one of the highest incidence of cholesterol gallstones in the world (Ref. 102). In a study that included twenty healthy 18 to 22 year old Chilean men (described in Table II) consumption of a diet (3219 calories) that contained 120 g per day of legumes reduced LDL-cholesterol (16 percent). Biliary cholesterol saturation increased significantly in 19 of 20 subjects receiving the legume-enriched diet. The authors suggest that the results are consistent with the hypothesis that legumes, (possibly due to nondigestible, saponins) are a potential risk factor for cholesterol gallstone diseases.

b. *Polyunsaturated fats.* Safety concerns associated with consumption of diets enriched in polyunsaturated fats include the following: Long term and increased consumption of polyunsaturated fats may alter membrane fluidity, which in turn, could alter cell membrane function with as yet, undefined results; may decrease levels of high density lipoprotein (a lipoprotein associated with decreased CHD risk) and increase in serum triglycerides (also as yet no firm conclusions); and may increase predisposition to or frequency of certain types of cancer. (In a companion document published elsewhere in this issue of the **Federal Register**, the relationship of dietary lipids, including unsaturated fatty acid such as polyunsaturated fatty acid, and cancer is reviewed relative to health claims.)

It has been suggested that polyunsaturated fats increase formation of lipid hydroperoxides, which in turn could alter or damage cell membranes. Both native and oxidized LDL-cholesterol are hypothesized to cause endothelial cell membrane injury, thus initiating atherogenesis by potentially increasing platelet adherence to blood vessel walls (Ref. 20 and 132). Other dietary components may influence cell membranes also.

In a review article, Steinberg (Ref. 132), pointed out that in vitro studies have demonstrated that oxidized LDL-cholesterol, perhaps resulting from increased hydroperoxides from polyunsaturated fats, is taken up 10 times faster by macrophages [large cells that engulf foreign particles] than unoxidized or native LDL-lipid. Furthermore, antioxidants such as vitamin E inhibited the peroxidation of polyunsaturated fat-LDL-cholesterol in vitro.

Berry (Ref. 6) reported the effects of diets enriched in either monounsaturated fat (oleic acid) or as polyunsaturated fat (linoleic acid) in 26 healthy male college students on blood cholesterol levels and concentration of oxidized LDL-cholesterol. The fat and saturated fat content of both diets was 32 and 8 percent of total calories, respectively. Approximately 17 percent of calories were from monounsaturated

of polyunsaturated fats. Each dietary treatment period lasted for 12 weeks and a 4-week Yeshiva diet was eaten during a 4–week cross-over period between diets. Compliance to the diets was assessed by measurement of fatty acid composition of red blood cell membranes. On the positive side, compared to baseline levels, total cholesterol was significantly reduced by 10 percent consumption of the monounsaturated diet and by 16 percent from consumption of polyunsaturated enriched diet. On the negative side, thiobarbituric acid-reactive substances (i.e., lipid peroxides) in blood increased significantly in the blood (LDL-cholesterol) of subjects who consumed the diet enriched in polyunsaturated fat. The authors suggested that monounsaturated fatty acids may be preferable because they are a poorer substrate for lipid peroxidation than polyunsaturated fatty acids. Other studies reviewed, which examined the effect of dietary polyunsaturated fats on serum lipids including HDL-cholesterol, are found in Table II.

c. *Persons with hypertriglyceridemia.* Although high blood cholesterol levels of lipids known as triglycerides (hypertriglyceridemia) has often been associated with increased risk of cardiovascular disease, the significance of this observation remains controversial (Ref. 20). Dietary changes including increased intakes of simple carbohydrates when fat intakes are decreased may unfavorably alter this condition (Ref. 20).

E. Conclusions

The conclusions of the reviews by the Federal government and by recognized scientific bodies that high blood levels of blood cholesterol and LDL-cholesterol are a cause have been confirmed and strengthened by recently published reports (Refs. 12, 14, 16, 17, 27, 38, 42, 76, 85, 86, 87, 106, 108, 109, 128, 131, 137, and 146). Additionally, earlier conclusions that lower levels in blood cholesterol are associated with the decreased risk of CHD have also been confirmed by recent reports including those of Sprakfa et al. (Ref. 128) and others (Refs. 12, 14, 16, 42, 76, 85, 86, 106, 128, 137, and 146). Estimates from new analysis of epidemiologic data suggest that a one mg per ml increase in serum cholesterol sustained for many years increases CHD risk by about 1.5 percent (Ref. 78). Significant reduction in serum cholesterol (greater than 5 mg per dL) decreases CHD mortality in men and women.

The conclusions of the Federal government and other reviews by recognized scientific bodies that substantial evidence from animal and human studies shows that consumption of dietary fats, especially saturated fats and cholesterol, are highly correlated with elevated blood total and LDL-cholesterol levels and increased risk of CHD were recon firmed and strengthened by research published subsequent to those reports. Recent cross-sectional and prospective studies confirm these conclusions by reporting significant correlations between dietary intakes of saturated fat and cholesterol and increased serum cholesterol (Refs. 5, 17, 28, 68, 134, and 139).

The Federal government reports and other reviews prepared by recognized scientific bodies noted the multifactorial nature of CHD. Factors included high serum cholesterol and LDL-cholesterol, high blood pressure, family history of CHD, cigarette smoking, obesity, sedentary lifestyle, and diabetes were identified as major risk factors.

Diets rich in total fat, saturated fat, and cholesterol increase total serum cholesterol and LDL-cholesterol (Refs. 17, 18, 19, 44, 51, 53, 54, 67, 103, 121, 139, and 140). Estimates from clinical trials and metabolic ward studies suggest that lowering intake of saturated fatty acids by 7 percent of total calories and accompanied by declines in blood cholesterol of 10 to 14 percent should decrease the risk of premature CHD over a decade by about 20 percent, or over a lifetime of 30 percent (Ref. 78).

Potential safety issues relate to possible changes in the relative composition of and amount of fats in the U.S. food supply. Because of lack of long-term safety data on increased consumption of polyunsaturated fats and trans-fatty acids, the Federal government and other reviews by recognized scientific bodies recommend that dietary consumption of polyunsaturated fatty acids remain at current intake levels of 7 percent of calories and should not exceed 10 percent of total calories (Refs. 20, 35, and 78). Intakes of trans-fatty acids were also recommended not to exceed current levels (Ref. 78).

The diet-CHD relationship is very strong and consistent for saturated fat and less so for cholesterol. Diets high in saturated fat and cholesterol are associated with elevated levels of blood total and LDL-cholesterol and consequently of risk of CHD. Diets low in total fat and cholesterol facilitate a reduction in saturated fat and cholesterol intakes and thus are also recommended as useful for lower blood cholesterol levels and for reducing the risk of CHD. A general population approach to reduce total dietary saturated fat, total fat, and cholesterol has been recommended as a practical goal for reducing blood cholesterol and risk of CHD as an achievable goal.

F. Tentative Decision To Authorize Health Claim and Label Statements: Dietary Lipids and Cardiovascular Disease

The agency reviewed the conclusions reached by the Federal government and other reviews by recognized scientific bodies, recent review articles, and the pertinent human and nonhuman primate studies published since 1988. The agency also considered all comments received in response to the request for data and information on the topic of lipids and cardiovascular disease. The totality of the scientific evidence provides strong and consistent support that diets high in saturated fat and cholesterol are associated with elevated levels of blood cholesterol and LDL-cholesterol and with risk of CHD. The general public health support of this concept, as evidenced by all recent dietary guidelines from both the government and other recognized scientific bodies, demonstrates that there is clear, significant agreement among experts qualified by training and experience to evaluate such evidence that the relationship between saturated fat and cholesterol, to blood cholesterol levels and, thus to decreased risk of CHD is particularly strong.

The prevalence of CHD is high in the U.S., and the associated medical and other costs are also high. About 27 percent of adults (male and female; black and white) aged 20 to 74 years of age have blood cholesterol levels in the "high risk" category (total cholesterol greater than 240 mg per dL and LDL-cholesterol greater than 160 mg per dL) (Ref. 119). Another 14 percent have "borderline high" cholesterol levels (total cholesterol between 200 to 239 mg per dL and LDL-cholesterol between 130 to 159 mg/dL) in combination with two or more risk factors. The majority of the American population would benefit from decreased consumption of dietary fat and cholesterol. Extrapolating from the 1986 population data, these observations suggest that 64 million Americans over 20 years of age are candidates for medical advice and intervention. For individuals who have high blood lipid levels, estimates of benefits to be derived from decreased serum lipids include an 8 percent reduction in total cholesterol resulting in a 19 percent reduction in myocardial infarction, and a 7 percent reduction in all cause mortality (Ref. 141).

Dietary fat intakes by the U.S. population are generally considered to be higher than desirable (Refs. 20, 29, 31, 33, and 35). Dietary estimates for American adults show, that average that saturated fat intakes of American adults are about 13 percent of calories, total fat intakes are about 37 percent of calories, and average cholesterol intakes range from 300 to over 40 mg daily for adult women and men. The current intakes of saturated fat and total fat are currently well in excess of recommended goals of less than 10 percent and 30 percent of calories, respectively. Current cholesterol intakes of adult men also exceed recommended goals. The feasibility of meeting recommended fat intakes by the general population was evaluated by a health survey which included 10,348 American men aged 18 and older (Ref. 116). The study results suggested that American adults can successfully follow a low saturated fat, low cholesterol diet without formal consultation with health professionals.

Browner et al. (Ref. 13) made statistical estimates on CHD mortality and total mortality if all Americans (across all ages, sex and race subgroups) reduced total fat intake to 30 percent of total calories as proposed by the Federal government guidelines and health care professionals. The estimates assumed optimal dietary compliance, without allowing for other risk factors or medical intervention. Under these limitations, Browner et al. (Ref. 13) estimated that serum cholesterol levels would decrease by 20 mg per dL. The estimated reduction in risk of CHD mortality was reported to be 5 percent in the elderly and up to 20 percent in younger people. This reduction was projected to result in a 2 percent decrease in all cause mortality. Each individual, based on a 1986 census data, would increase his or her life expectancy by 3 to 4 months. For other individuals, the increase in life expectancy and quality of life would be much greater.

Thus, FDA believes health claims conforming to the proposed regulation will assist those of the general population who wish to select foods reduced in saturated fats, total fats, and cholesterol for reduction in serum cholesterol level and therefore, the risk of CHD.

No deficiency of essential fatty acids or cholesterol or other adverse effects is anticipated from the decreased consumption of dietary lipids (saturated fat, cholesterol and total dietary fat) to levels proposed by the Federal government and other reviews recognized by scientific bodies.

III. Proposed Regulation

A. Scope of Regulation

Based on the totality of the evidence, FDA has tentatively determined that there is and significant scientific agreement among experts qualified by training and experience to evaluate such claims, that consumption of diets high in saturated fats and cholesterol increases total and LDL-cholesterol levels and thus the risk of developing CHD.

The specific health claim topic, as contained in section 3(b)(1)(A)(vi) of the 1990 amendments, is "dietary lipids and cardiovascular disease". FDA, however, limited its review to saturated fats and cholesterol, and to CHD. The agency considered these limitations necessary because of the extremely large volume of research available on the broad topic of dietary lipids and cardiovascular disease, because the scientific data most explicitly supports the lipid nutrient relationship to blood cholesterol levels and thus CHD and finally because CHD is the most serious, primary, and earliest form of cardiovascular disease. In addition, FDA based its selection of saturated fats and cholesterol among the dietary lipids on the conclusions of a number of comprehensive reports by the Federal government and the National Academy of Sciences which identified high levels of these dietary lipids with high blood cholesterol, which is as causally related to CHD. FDA recognizes that considerable research is being conducted on possible roles of other dietary lipids than saturated fats and cholesterol and the risk of CHD. However, time constraints precluded thorough review of these other lipids. Petitions, in accordance with proposed requirements for health claims petitions prohibited elsewhere in this issue of the **Federal Register**, may be submitted to the agency to request that the relationship of other dietary lipid components to CHD, and that other aspects of cardiovascular disease,

B. Relationship Between Dietary Lipids and Cardiovascular Disease and the Significance of the Relationship

Proposed § 101.73(a)(1) describes the relationship between dietary lipids and cardiovascular disease. Proposed § 101.73(a)(2) describes the significance of the nutrient-disease relationship for the U.S. population.

Cardiovascular disease, of which CHD is the most frequently reported manifestation, caused nearly one of every two deaths in the United States in 1987. More than 1 million individuals suffer heart attacks each year, and more than 500,000 die from complications associated with CHD. In contrast, it is estimated that for every 1 percent drop in serum cholesterol levels, there will be, on average, a 1.5 to 2 percent drop in incidence in CHD.

Current dietary guidelines recommend that saturated fat intakes be at or below 10 percent of calories and preferably at 7 percent of calories, and that cholesterol intakes be at or below 300 mg per day. Adults in the U.S. consume, on average, 13 percent of calories as saturated fats. Presently, intakes of dietary cholesterol by American women are at the goal of 300 mg per day but are higher (approximately 400 mg per day) for American adult men.

CHD is associated with a number of risk factors: high blood cholesterol levels, obesity, high blood pressure, cigarette smoking, a family history of heart disease, and physical inactivity. Currently, average serum cholesterol levels in the U.S. are 213 mg per dL for adults. Approximately 25 to 30 percent of the adult U.S. population have serum cholesterol levels above 200 mg per dL.

The significant public health benefits to be derived from decreased consumption of foods high in saturated fats and cholesterol with respect to decreased morbidity and mortality from CHD are based on conclusions reached by Federal government documents such as "The Surgeon General's Report on Nutrition and Health" (Ref. 35) and other reviews by recognized scientific bodies including the National Academy of Sciences' "Diet and Health" (Ref. 20) and reports from the NCEP (Refs. 31, 32, 33, and 34) and supported by FDA's review of the more recent evidence.

C. General Requirements

1. Conformity With 21 CFR 101.14 (General Requirements for Health Claims on Food)

In § 101.73(a)(3)(i), FDA is proposing that health claims relating to an association between dietary lipids (specifically saturated fats and cholesterol) and CHD may be made on the label or in the labeling of a food so long as all the general requirements set forth in § 101.14, proposed elsewhere in this **Federal Register** document, are met. Proposed § 101.14 sets forth such matters as the levels of fat, saturated fat, cholesterol and sodium that would disqualify a food from bearing a health claim and the manner in which a claim must be presented.

2. Qualifying Nutrients: Saturated Fat and Cholesterol

In § 101.73(a)(3)(ii), FDA is proposing that a health claim relating diets low in saturated fats and cholesterol to

reduced risk of CHD would be prohibited unless the food that is to bear a claim meets the requirements of the definitions for "low saturated fat," and "low cholesterol." These requirements are set forth in proposed § 101.62.

The evidence for the association between intake of dietary lipids and blood cholesterol levels, and ultimately to the risk of developing CHD, is strongest for dietary saturated fats and cholesterol. In the proposed "General Requirements for Health Claims for Food" (published elsewhere in this issue of the **Federal Register**), FDA is proposing that for a substance, such as dietary saturated fat or cholesterol, for which decreased levels are needed to achieve dietary goals, the substance be at a low enough level in a food that is a candidate for a claim to justify the claim. It is further proposed that a level that meets the proposed levels for the term "low" be the deciding criteria. In a companion document on "Definitions of Nutrient Content Claims for the Fat, Fatty Acid, and Cholesterol Content of Foods," FDA is proposing that the food contain 1 g or less of saturated fatty acids per label serving size and per reference amount customarily consumed and not more than 15 percent of calories from saturated fatty acids. In that same document, FDA is also proposing that a food can qualify for a "low cholesterol" claim if it contains 20 mg or less of cholesterol per label serving size, per reference amount customarily consumed, and per 100 g of food.

The linkage of dietary saturated fat to blood cholesterol, however, raises questions as to the definition of saturated fats. In another document published elsewhere in this issue of the **Federal Register** ("Supplementary Mandatory Nutrition Labeling"), FDA is proposing to retain the current definitions of saturated fats for nutrition labeling purposes. Saturated fats are defined as the sum of lauric, myristic, palmitic, and stearic acids (C12–C18). Several recent reviews by recognized scientific bodies (Ref. 20) and more recent studies (Refs. 54 and 56) have suggested that the serum cholesterol-raising properties of saturated fats are limited primarily to C12 through C16, and that C18 does not have an appreciable effect on serum cholesterol levels. In response to early agency proposals on content claims for cholesterol and saturated fat (Ref.), and in response to FDA's request for scientific data and information relating to health claims (Ref.), FDA received numerous comments from the food industry requesting that declaration of saturated fat for nutrition labeling purposes be limited to the sum of the three saturated fats most clearly related to serum cholesterol-raising effects (i.e., lauric, myristic, and palmitic).

FDA is aware of this rapidly evolving research area but is proposing not to limit the definition of saturated fats to those most related to adverse effects on serum cholesterol. As noted previously, elevated blood cholesterol is not the only risk factor related to CHD and ultimately to cardiovascular disease. Other saturated fats have also been implicated to increase risk for cardiovascular disease, particularly relative to thrombogenic effects (blood clotting) and related effects which affect blood flow (Ref. 20). For this reason, FDA is proposing not to limit declaration of saturated fats to those related to blood cholesterol.

3. Additional Requirements for Saturated Fats

In proposed § 101.73(a)(3)(iii), FDA is proposing that health claims relating diets low in saturated fat and cholesterol to decreased risk of CHD must also contain saturated fat at levels less than 1 g per 100 g or food.

FDA, as noted above, is proposing to allow the use of the term "low saturated fat" if the food contains 1 g or less of saturated fat per label serving size and per reference amount customarily consumed and not more than 15 percent of calories from saturated fatty acids (see document "Definitions of Nutrient Content Claims for the Fat, Fatty Acid, and Cholesterol Content of Foods" published elsewhere in this use of the **Federal Register**). FDA is proposing the latter criterion in lieu of one based on one tied into the amount of saturated fat per 100 g of food. FDA has explained that it is doing so because the calorie density criterion will allow consumers to make comparisons among fats and oils and thus to aid them in choosing those products lowest in saturated fats when selecting from a category of products whose composition is essentially 100 percent fat. However, for health claims, FDA is concerned that a health claim linking saturated fat and reduced risk of CHD might inappropriately encourage increased consumption of fats and oils with the expectation that they have added health benefit. This is contrary to the recommendations of most current dietary guidelines which unanimously recommend reductions in total fat as well as saturated fat. Thus, FDA is proposing to require in § 101.72(a)(3)(iii) that a food must contain saturated fat at a level of less than 1 g per 100 g of food to bear a health claim.

4. Other Qualifying Nutrients: Low Total Fat

In § 101.73(a)(3)(ii), FDA is also proposing that health claims relating diets low in saturated fat or cholesterol to lower blood cholesterol levels and reduced risk of CHD are prohibited unless the food also meets requirements for a "low" claim relative to total fat content as proposed in the document "Definitions of Nutrient Content Claims for the Fat, Fatty Acid, and Cholesterol Content of Foods" published elsewhere in this issue of the **Federal Register**). In that document, FDA is proposing to define "low total fat" as 3 g or less of fat per label serving size, per reference amount customarily consumed, and per 100 g.

While total fat is not directly linked to increased risk of CHD, it may have significant indirect effects. Low total fat diets facilitate reductions in intakes of saturated fat and cholesterol to recommended levels. Furthermore, obesity is a major risk factor for CHD, and dietary fats, which have more than twice as many calories as proteins and carbohydrates, are major contributors to total calorie intakes. For many adults, maintenance of desirable body weight is more readily achieved with moderation of intake of total fat. The issue of dietary fat and risk of cancer is addressed elsewhere in this issue of the **Federal Register**. This approach is also most consistent with the U.S. Dietary Guidelines and other dietary guidance that recommends diets low in saturated fat, total fat, and cholesterol.

5. Examples of Qualifying Foods

FDA used the criteria for dietary lipids content and sodium to identify foods that would likely be able to bear health claims about the relationship of saturated fat and cholesterol to effects on blood cholesterol, and thus, to risk of CHD. Examples of foods qualifying for a health claim include most fruits and vegetables; skim milk products; sherbets; most flours, grains, meals and pastas (except for egg pastas); and many breakfast cereals. FDA believes that many of these foods are appropriate foods for health claims. However, the agency is concerned that some foods with no apparent nutritive value other than calories (such as candies) would also qualify. FDA solicits comments and suggestions on how to restrict the use of fat/CHD health claims to foods that are generally recognized as part of healthy diets.

D. Specific Requirements for Health Claims

1. Health Claims: Requirements

In § 101.73(a)(4)(i), FDA is proposing that health claims relating dietary lipids to blood cholesterol and CHD must make clear diets low in saturated fat and cholesterol, will reduce blood cholesterol levels which in turn will reduce the risk of developing CHD.

This requirement is based on the effect, as well as the strength, of the scientific evidence regarding the relationship of dietary lipids, especially saturated fatty acids and cholesterol, to risk of CHD. This relationship is extensively documented and summarized in Federal government reports, in other reviews by recognized scientific bodies, and in the science review presented in this document. It shows the intermediate effect of the dietary lipids on blood cholesterol levels and of the blood levels on the risk of CHD. This intermediate effect must clear in any health claim.

2. Variability in Response to Dietary Modification

In § 101.73(a)(4)(ii), FDA is proposing to require that health claims relating diets low in saturated fats and cholesterol to reduced risk of CHD state that most but not all people will reduce blood cholesterol levels with a decreased intake of saturated fatty acids and cholesterol. These responses are variable between, among, and even within individuals, and the variability is greater with respect to dietary cholesterol than to saturated fats.

3. Interchangeable Terms

The scientific evidence most strongly supports a link between dietary saturated fats and cholesterol and CHD. In proposed § 101.73(a)(4)(iii), the agency is proposing to allow manufacturers to use the terms of "CHD" or "heart disease" to name the disease. These terms are terms most commonly used to describe the disease and therefore are expected to be the most understandable for the consumer. Fewer terms are also expected to minimize consumer confusion.

Similarly, to reduce confusion and misleading declarations, the agency is proposing to require the use of the terms "blood cholesterol" or "total blood cholesterol" rather than the more technically correct terms "serum," "plasma cholesterol," or "LDL-cholesterol." The term "blood cholesterol" is more commonly used by consumers and is consistent with terminology in most dietary guidelines. FDA is also proposing to require the use of the dietary terms "saturated fat" and "cholesterol" because these terms are consistent with the terminology on the nutrition label and, therefore, should be less confusing to consumers.

4. Multifactorial Nature of the Disease

In § 101.73 (a)(4)(iv), the agency is proposing to require that health claims identify other risk factors (in addition to elevated blood cholesterol) for CHD. Other modifiable risk factors include high blood pressure, cigarette smoking, physical inactivity, and obesity. These various risk factors appear to act in concert to increase risk. Their effects are at best additive and may in some cases be multiplicative. The agency believes that this additional information provides a basis for the nutrient-disease relationship and will increase consumer understanding of the numerous factors that contribute to risk of CHD.

E. Optional Requirements

In § 101.73(a)(5)(iii), the agency is proposing to allow manufacturers to provide accurate, up-to-date, factual information about the incidence, prevalence or frequency of, morbidity, mortality, cost of health care, etc. data including socio-economic status or educational level, age, sex, or race relating to risk of the CHD. The intent is to provide consumers with such information as will help them understand the seriousness of CHD in the U.S. The source of such information should be the most current and commonly used data from the National Center for Health Statistics. Use of such data will maintain consistency in estimates or statistical data used in the health claim. The source of the data used in the health claim must be identified.

F. Model Health Claims

In proposed § 101.72, FDA is providing four model health messages to help manufacturers to understand the requirements of proposed § 101.72(a) and to help them understand the type of message that FDA considers to be necessary and appropriate.

IV. Appendix to the Preamble—Consumer Summary on Dietary Lipids and Cancer and Dietary Lipids and Coronary Heart Disease

The following appendix is a proposed consumer summary to provide factual information in an easily understandable manner, to assist the consumer in understanding the seriousness of the diet (dietary lipids)/disease (cardiovascular disease) relationship. The role or relationship of dietary lipids (particularly saturated fats and cholesterol) to cardiovascular disease (particularly CHD) is discussed. FDA solicits comments on this document as explained in the proposal on general requirements for health claims published elsewhere in this issue of the **Federal Register.**

Appendix—Dietary Lipids and Cancer and Dietary Lipids and Coronary Heart Disease

Under the provisions of the recent Nutrition Labeling and Education Act, manufacturers may put clear information on the food label about the relationship between a nutrient, such as fat or cholesterol, and a disease or health-related condition. To prevent consumers from being misled, the Food and Drug Administration (FDA) allows only truthful label statements about diet and health relationships that are firmly supported by the current scientific evidence. There is agreement that the scientific evidence is strong enough to allow health claims about the association between total dietary fat and the risk of some types of cancer and the association between dietary saturated fat and cholesterol and the risk of CHD.

Many consumers have said that health claims on food labels could be useful to them in making improvements in their diets. However, label space is often limited. Therefore, this pamphlet provides information about diet and health claims that supplements what you may see on food labels.

In addition to the association between fat and cancer and between saturated fat, cholesterol and heart disease, FDA is allowing health claims about calcium and osteoporosis and sodium and hypertension. For information about these other diet and health relationships, write to: to be inserted.

What is Coronary Heart Disease?

A common usage term for coronary heart disease is heart disease. Coronary heart disease encompasses the heart muscle and its supporting blood vessels. Complications from heart disease results from narrowing of blood vessels (medically called atherosclerosis) and decreased flow of blood to various parts of the body. Myocardial infarction or MI is a medical term used to describe a heart attack.

Atherosclerosis occurs because of raised fatty or fibrous deposits (plaque) that develop in the walls of blood vessels in the affected area. The process of plaque development is gradual, and often begins in childhood.

What is Cancer?

Cancer is not one disease, but more than 100 different diseases. In each of these diseases, cells begin to grow out of control at one site in the body, and these abnormal cells spread to other parts of the body.

Why Are Heart Disease and Cancer Major Public Health Concerns?

Coronary heart disease and cancer are public health concerns because they are the two leading causes of death in this country. Illness and death from these diseases cost billions of dollars in health care costs and in lost work. Moreover, early deaths from these two diseases cheat many victims of valuable years of life.

Despite the recent sharp decline in the death rate from this condition, coronary heart disease still accounts for the largest number of deaths in the U.S. Cancer is the second leading cause of death in this country. The leading causes of cancer death are lung cancer, colorectal cancer, breast cancer, and prostate cancer.

What Causes Cancer and Coronary Heart Disease?

Both of these diseases are caused by a combination and interaction of multiple environmental, behavioral, social, and hereditary factors. It is clear that diet, one of the environmental factors, plays an important role in the development of these diseases.

Heredity and other factors, including elevated blood serum cholesterol, cigarette smoking, high blood pressure, obesity and inactive life style, are known to increase a person's risk of developing coronary heart disease. Elevated blood cholesterol, one of the major risk factors for coronary heart disease, is associated with excess fat, especially saturated fat, and cholesterol in the diet.

Many studies have established a strong association between consuming a diet high in saturated fat and cholesterol and increased risk of coronary heart disease. High saturated fat and cholesterol diets are estimated to be associated with one-third of the cases of coronary heart disease reported in this country.

The way diet affects blood cholesterol varies among individuals. However, blood cholesterol does increase in most people when they eat a diet high in saturated fat and cholesterol and excessive in calories. Of these, saturated fat has the greatest effect; dietary cholesterol has less.

Cancer has many causes and several stages in its development. The risk factors for developing cancer include a family history of a specific type of cancer (such as breast, prostate or colon cancer), cigarette smoking, alcohol consumption, radiation, and dietary factors.

Currently, the strongest scientific evidence relating diet to cancer is that the amount of total fat in the diet may have a relationship with cancer. In particular, many experts agree that a high fat diet may influence the risk for developing breast, colon, and prostate cancers.

Not enough is known currently for scientists to decide whether different kinds of fats (animal or vegetable; saturated or unsaturated) may be responsible for an increased risk of developing cancer.

Because of scientific agreement that reducing total fat and saturated fat is likely to lower the rates of these two major chronic diseases, it is recommended that Americans 2 years of age and older choose a diet low in total fat and saturated fat. Animal products are the source of all dietary cholesterol. Eating less fat from animal sources will help to lower the cholesterol as well as the saturated fat in your diet.

Do Most People Get Too Much Fat, Saturated Fat and Cholesterol in What They Eat?

The average U.S. diet, it's estimated, contains about 37 percent of calories from total fat, 13 percent of calories from saturated fat, and 360 mg of cholesterol per day. Health experts recommend diets that contain 30 percent or less of calories from total fat, 10 per cent or less of calories from saturated fat, and 300 mg or less of cholesterol a day. The U.S. Public Health Service has set a national health goal that all persons who are 2 years of age and older consume these levels of fat and cholesterol by the end of this decade.

How Do You Learn How Much Fat and Cholesterol Foods Contain?

You may or may not be able to tell that there's fat in a food by looking at it. Butter, margarines, shortenings, and oils are the more obvious sources of fat. In other foods, such as cheese, baked goods, nuts, and salad dressings, the fat isn't as easily detected. Cholesterol content is not obvious at all in foods.

A good way to learn about fat and cholesterol content is to read nutrition labels. Most foods now have nutrition information on their labels.

The amounts of total fat and saturated fat in a serving of food are listed in grams (g) on the nutrition label. Cholesterol is listed in milligrams (mg).

"Daily values" for fat, saturated and cholesterol also appear on food labels. These numbers have been established by FDA for several nutrients that are important in diet and health relationships. The daily values are to help you learn how the amount of a nutrient in a serving of food relates to a reasonable amount for the day.

The daily value for total fat is 75 g, and for saturated fat is 25 g. That mean total fat for a day of 75 g, of which no more than 25 g should be from saturate fat. These numbers are based on a 235(calorie diet that has 30 percent of calories from fat and 10 percent from saturated fat. A 2350–calorie diet is about the calories recommended for an adult woman.

If you consume a different number of calories a day, it's not hard to figure ou your own daily values for total fat and saturated fat. First, multiply the numbe of calories you consume by 30 percent (for example, 2000×.30=600). Then divide that number by nine, which is th number of calories each g of fat provide (600 divided by 9=67 g of fat a day). Repeat for saturated fat (2000×.10=20(200 divided by 9=22 g of saturated fat a day).

The daily value for cholesterol is 300 milligrams, which is an upper limit that generally recommended for healthy people. A food that contains 150 milligrams of cholesterol per serving, therefore, would provide about half of the daily value for cholesterol.

What Do Label Claims About Fat and Cholesterol Mean?

In addition to the amount of fat and cholesterol listed on the nutrition label, you may see other claims about fat and cholesterol content on some food packages. There are two types of these claims—nutrient content claims and health claims.

Nutrient content claims describe the amount of fat, saturated fat or cholesterol a food contains. These type of claims can be used on a label only if food meets several definitions established by FDA.

Cholesterol claims

- A "cholesterol free" food has less than 2 milligrams of cholesterol and 2 grams or less of saturated fat in a serving.
- A "low cholesterol" food has 20 milligrams or less of cholesterol in a serving and in 100 grams of food and 2 grams or less of saturated fat in a serving.
- A "reduced cholesterol" food has it cholesterol content reduced by 50 percent or more compared to the regula

food product and contains 2 g or less of saturated fat in a serving.

Cholesterol claims may be made only on foods that contain a limited amount of fat (no more than 11.5 g per serving and per 100 g) unless the claim also tells the total amount of fat, for example, "cholesterol free, contains 12 g of fat per serving."

Fat claims

- A "fat free" food has less than a half g of fat in a serving and no added fat or oil.
- A "low fat" food has 3 g or less of fat in a serving.
- A "reduced fat" food has a 50 percent or more reduction in fat with at least a 3 g reduction in fat content.
- A "low saturated fat" food has 1 g or less of saturated fat in a serving and no more than 15 percent of its calories from saturated fat.
- A "reduced saturated fat" food has its saturated fat content reduced by 50 percent or more compared to the regular food product with at least a 1 g reduction in fat.

Also, the labels of some foods in which fat or cholesterol has been significantly reduced, but not enough to meet the definitions above, may have a statement that tells how much less fat or cholesterol the product contains than a comparable product; for example, "This pound cake contains 40 percent less fat than our regular pound cake."

Foods such as fruits and vegetables that meet the definitions for fat or cholesterol without special processing may have claims on them. However, the label must say that fat or cholesterol isn't usually present in the food, for example, "broccoli, a fat-free food," "frozen perch, a low fat food," or "raspberries, a low saturated fat food."

Health claims are those made about the relationship between the amount of a nutrient you eat and the risk of a disease, for example, between total fat and cancer or between saturated fat and cholesterol and heart disease.

Health claims about the relationship between fat and cholesterol and heart disease can only be made on products that are low in saturated fat and cholesterol, and have 15 percent or less of their calories from fat. To make a health claim, the product also cannot contain another nutrient that increases the risk of a diet-related disease other than atherosclerosis, for example, a high amount of sodium which has a relationship to high blood pressure.

Health claims about the relationship between fat and cancer can be made only on foods that are low in fat and do not contain another nutrient that increases the risk of a diet-related disease other than cancer.

These are some of the kinds of foods on which you may see health claims about nutrients related to cancer and heart disease: fruits, fruit juices, vegetables, breakfast cereals, dried peas and beans, skim milk, pasta products, and diet salad dressings.

Other Risk Factors for Cancer and Heart Disease

Coronary heart diseases and cancer are complex diseases with multiple causes, and they (usually) develop over a long period of life. Hereditary as well as environmental factors contribute to the risk for developing these diseases. In addition to practicing good nutrition, several other controllable factors are part of a healthy lifestyle and may help to decrease your chances of cardiovascular disease and cancer. These include maintaining a healthy body weight and good physical fitness, not smoking cigarettes, drinking only in moderation if at all, and not abusing drugs.

Facts to Keep in Mind

- It's the total combination of foods that you eat regularly—both the kinds and the amounts—that's important in terms of good nutrition. Eating a particular food or a specific food isn't a magic key that will assure you have a more healthful diet.
- Eating a healthy diet, in itself, doesn't guarantee good health. A healthy diet, however, is an important part of a healthy lifestyle.
- In addition to what you eat, many factors may be related to your own chance of developing a particular disease, for example, your heredity, your environment, and the health care that you get. Our knowledge about most diet-health relationships is incomplete, and will improve as scientific knowledge increases. However, enough is known today about some of these relationships to encourage specific dietary practices that are believed to be beneficial.

V. References

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

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Dementia with Advancing Age, Epidemiologic Considerations," *Archives of Internal Medicine*, 151:240–244, 1991.

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150. DHHS and USDA, "The Relationship Between Dietary Cholesterol and Blood Cholesterol and Human Health and Nutrition, A Report to the Congress," Pub. L. 99–190, Subtitle B, Section 1453, 1926.

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VI. Environmental Impact

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

VII. Economic Impact

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

VIII. Effective Date

FDA notes, however, that in section 10(a)(3)(B) of the 1990 amendments, Congress provides that if the Secretary, and by delegation FDA, finds that requiring compliance with section 403(q) of the act, on mandatory nutrition labeling, or with section 403(r)(2) of the act, on nutrient content claims, 6 months after publication of the final rules in the **Federal Register** would cause undue economic hardship, the Secretary may delay the application of these sections for no more than 1 year. In light of the agency's tentative findings in its RIA that compliance with the 1990 amendments by May 8, 1993, will cost $1.5 billion, and that 6 month and 1 year extensions of that compliance date will result in savings that arguably outweigh the lost benefits, FDA believes that the question of whether it can and should provide for an extension of the effective date of sections 403(q) and (r)(2) of the act is squarely raised.

FDA has carefully studied the language of section 10(a)(3)(B) of the 1990 amendments and sees a number of questions that need to be addressed. The first question is the meaning of "undue economic hardship." FDA recognizes that the costs of compliance with the new law are high, but those costs derive in large measure from the great number of labels and firms involved. The agency questions whether the costs reflected in the aggregate number represent "undue economic hardship."

Therefore, FDA requests comments on how it should assess "undue economic hardship." Should it assess this question on a firm-by-firm basis, as was provided in the bill that passed the House Committee on Energy and Commerce (H. Rept. 101–533, 101st Cong., 2d sess., 24 (1990)), an industry-by-industry basis, or should it assess this question on an aggregate basis? If the agency should take the latter approach, comments should provide evidence that would permit the agency to make a determination that there is "undue economic hardship" for most companies. FDA also points out that assessing hardship on a firm-by-firm basis would likely be extremely burdensome because of the likely number of requests.

FDA will consider the question of the meaning and appropriate application of section 10(a)(3)(B) of the 1990 amendments as soon as possible after the comment period closes. The agency intends to publish a notice in advance of any final rule announcing how it will implement this section to assist firms in planning how they will comply with the act. The early publication of this notice is to assist firms in avoiding any unnecessary expenses that could be incurred by trying to comply with a compliance date that may cause "undue economic hardship."

IX. Comments

Interested persons may, on or before February 25, 1992, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. to 4 p.m., Monday through Friday.

In accordance with section 3(b)(1)(B) of the 1990 amendments, FDA must issue by November 8, 1992, final regulations for mandatory nutrition labeling. If the agency does not promulgate final regulations by November 8, 1992, the 1990 amendments provide that the regulations proposed in this document shall be considered as the final regulations. The agency has determined that 90 days is the maximum time that it can provide for the submission of comments and still meet this statutory timeframe for the issuance of final regulations. Thus, the agency is advising that it will not consider any requests under 21 CFR 10.40(b) for extension of the comment period beyond February 25, 1992. The agency must limit the comment period to no more than 90 days to assure sufficient time to develop a final rule based on this proposal and the comments it receives.

List of Subjects in 21 CFR Part 101

Food Labeling, Reporting and recordkeeping requirements.

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

PART 101—FOOD LABELING

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

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

2. New § 101.73 is added to subpart E to read as follows:

§ 101.73 Health claims: lipids and cardiovascular disease and lipids and cancer.

(a) *Coronary heart disease*—(1) *Relationship between dietary lipids (primarily saturated fat and cholesterol) and coronary heart disease:* Diets high in the lipid components, saturated fat and cholesterol are associated with increased levels of blood cholesterol and, thus, increased risk of developing coronary heart disease. Reductions in intake of saturated fats and cholesterol are associated with decreased levels of blood cholesterol and lower risk of developing coronary heart disease.

(2) *Significance of the relationship between saturated fat and cholesterol and risk of coronary heart disease.* The cost of coronary heart disease in the United States is considerable in terms of morbidity, mortality, direct health care expenditure and loss in productivity. Substantial improvements in the quality of life and significant reductions in health care costs can result from reducing the morbidity and mortality associated with coronary heart disease. Early management of risk factors for

coronary heart disease can aid in achieving this major public health goal for which national, population based recommendations to reduce risk of coronary heart disease and other forms of cardiovascular disease have been made. One of the major recommendations is to decrease consumption of dietary fat, especially saturated fat and cholesterol.

(3) *General requirements.* A health claim associating a diet low in saturated fat and cholesterol with decreased risk of coronary heart disease may be made on the label or labeling of a food provided that:

(i) All requirements set forth in § 101.14 are met;

(ii) A serving of the food meets the requirements of § 101.62 for:

(A) "Low saturated fat,"

(B) "Low cholesterol," and

(C) "Low fat."

(iii) The food contains 1 gram or less of saturated fat per 100 grams.

(4) *Specific requirements.* The health claim would be prohibited unless the following requirements are met:

(i) The health claim shall state that a diet low in saturated fat and cholesterol will reduce high blood cholesterol and, thus, reduce the risk of coronary heart disease.

(ii) The health claim shall state that a diet low in saturated fat and cholesterol will reduce high blood cholesterol in some individuals but not in all;

(iii) The health claim shall use the following terms:

(A) For the disease: coronary heart disease or heart disease;

(B) For lipid levels: Blood cholesterol or total blood cholesterol; and

(C) For dietary terms, saturated fat(s); or cholesterol.

(iv) The health claim may indicate that coronary heart disease is a multifactorial disease. It may identify major risk factors:

(A) A family history of coronary heart disease;

(B) Those who have elevated blood cholesterol levels;

(C) High blood pressure;

(D) Those who smoke cigarettes

(E) Those who are obese (greater than 30 percent above ideal body weight);

(F) Those who have diabetes; and

(G) Those who are physically inactive.

(5) *Optional information.* The health claim may provide the following information.

(i) The health claim may state that individuals with elevated blood cholesterol, a family history of coronary heart disease, or those with multiple risk factors for coronary heart disease should seek medical advice and guidance; and

(ii) The health claim may include information on the number of people in the United States who are at risk or who have been diagnosed as having coronary heart disease or may include information on morbidity and mortality associated with coronary heart disease. The sources of such information must be identified, and be current (as found in information from the National Center for Health Statistics).

(6) The following are four sample health claims that may be used in food labeling to describe the relationship between dietary lipids and cardiovascular disease:

Four Sample Health Claims

1. Diets low in saturated fat and cholesterol, as part of well balanced diets and healthy lifestyles, will reduce elevated blood cholesterol and lower the risk of developing heart disease in most individuals. Individuals at highest risk include those with a medical history of heart disease, hypertension, or who have blood cholesterol levels greater than 200 mg per dL. Other risk factors include: inheritance of premature coronary heart disease, smoking, obesity, diabetes mellitus, and sedentary lifestyle.

2. Heart disease is associated with many risk factors including: a family history of premature heart disease, high blood cholesterol, hypertension, cigarette smoking, obesity and consumption of diets high in saturated fat and cholesterol. A healthful diet low in saturated fat, total fat, and cholesterol will lower blood cholesterol and reduce the risk of heart disease in most people.

3. Developing heart disease depends upon many factors, including a family history of the disease, high blood cholesterol, high blood pressure, being overweight, cigarette smoking, lack of exercise, and diets high in some types of fat. A healthful diet low in saturated fat, total fat, and cholesterol and a healthy lifestyle will lower blood cholesterol levels and reduce the risk of heart disease in most people.

4. High blood cholesterol is a major cause of coronary heart disease. Other important factors are a family history of heart disease, being overweight, high blood pressure, and cigarette smoking. A healthy diet low in saturated fat, total fat, and cholesterol will lower blood cholesterol levels and reduce the risk of heart disease in most people.

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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

TABLE 1.—LIPIDS AND CARDIOVASCULAR DISEASE: EPIDEMIOLOGICAL STUDIES (SCIENCE SUMMARY UPDATE)

Reference	Study design	Study population	Duration	Test/Methods	Results	Comments and assessment
Abbot 1988 (Ref. 1).	Prospective, Framingham Study.	2425 men and women; 50 to 79 years; Multiple risk factors: BP, Wt, smoking, HDL-C, TC, estrogen.	12 year	N/A	Importance of HDL-C; possible to have high TC of which HDL-C make it high and have decreased risk of CHD; (men HDL-C 53 to 129 mg/dl or women 47 to 55 mg/dl reduce risk of CHD); HDL-C protect women who are above 50 years old HDL-C less than 46 mg/dl 6 times increased risk women of CHD for men less than 53 mg/dl results in 60 to 70% chance of MI.	Protective effect of HDL-C in men and women varies with age estimates relative risk reduction.

TABLE 1.—LIPIDS AND CARDIOVASCULAR DISEASE: EPIDEMIOLOGICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Test/Methods	Results	Comments and assessment
Burke 1991 (Ref. 15).	Cross-sectional	Minnesota residents 25 to 74 years old, both sexes; first survey in 1980 to 82 had a population of 3366; second survey in 1985 to 87 consisted of a population of 4645.	N/A	Part of the Minnesota Heart Survey. This survey is more focused upon examining concurrent community trends in awareness of heart disease and preventive factors Dietary survey methods are not discussed in this paper.	In both men and women, the distribution of cholesterol levels decreased from 1980 to 1982 to 1985 to 1987. The greatest decline in serum total cholesterol was observed in the 65 to 74 year olds.	The survey is not applicable to the questions of dietary causes of heart disease.
Bush 1988 (Ref. 17).	Prospective re-analysis of the relationship of diet to serum cholesterol in women.	Analysis of data for women from 9 prospective studies: (Framingham, Tel Aviv, NHANES) with emphasis on HDL-C.	variable	N/A	Women with greater than 265 mg/dl TC are at 3X greater risk of MI; HDL-C is strongly negatively correlated and is an independent predictor of CHD in women. For each 10 mg/dl reduction in HDL, there is a 50% decrease in MI; low cholesterol diet or high P/S diets in women decrease TC, LDL-C, and HDL-C; obese women have high TC, LDL-C and low HDL-C.	HANES survey showed no association between dietary and serum cholesterol
Dagenais 1990 (Ref. 27).	Prospective	4576 men, 35 to 64 years; Multi-factors; end points first event CHD, angina, MI, CHD death. Subjects free of heart disease at beginning of study.	12 year	Baseline history through questionnaire, complete medical evaluation to rule out CVD. Cardiologist diagnosed angina, enzyme levels, EKG, MI, autopsy data.	Adjusted data for age High serum cholesterol was positively correlated with the first coronary event, but not CHD mortality. Two-thirds of CHD incidence is due to elevated blood pressure, smoking and high serum cholesterol.	Since elevated BP is a risk factor in CHD, antihypertensive medications may be a confounding risk factor. Well-controlled.
Dyerberg 1989 (Ref. 40).	Cross-sectional study of dietary fats and serum lipids in two population groups (in Greenland and Denmark).	45 to 64 year old Danish men and Greenland Inuit men.	25 years of data.	Laboratory analysis of blood; morbidity data, which the author admits is not as good among the Inuits as the Danes.	Inuits: Fat energy, 33%; P/S ratio, .84; n-3 PUFA 14g/day Danes: Fat energy, 42%; P/S ratio, .24; n-3 PUFA, 3g/1 day. Although the Inuits have higher fat intake than Danes, Danes have a 13:1 incidence of acute MI, compared to Greenlanders. There is a highly significant difference (<.005) between the Danes and Inuits in all of the following parameters: cholesterol, triglycerides, LDL, VLDL, and HDL.	Uncontrolled for other risk factors, such as genetic and lifestyle differences.
Gramenzi 1990 (Ref. 51).	Case-control study of impact of diet on CHD.	Cases: 287 Italian women, with history of acute MI; average age 49; 649 Controls: patients from 30 hospitals.	5 years	Food frequency and lifestyle questionnaire.	Acute MI was strongly associated with frequency of consumption of meat, ham, salami, butter, total fat added to food and coffee. A slight inverse relationship was observed between consumption of fish, carrots, green vegetables and fresh fruit.	Questionnaire was verified by telephone in only 10% of cases. Insensitive dietary collection (Food frequency reported as low, medium, or high).

TABLE 1.—LIPIDS AND CARDIOVASCULAR DISEASE: EPIDEMIOLOGICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Test/Methods	Results	Comments and assessment
Kesteloot 1989 (Ref. 68).	Cross-sectional	Stratified random sampling in 42 counties of Belgium which yielded 5485 men and 4856 women.	Cross-sectional	Data on nutrition were obtained by a 24 hour food record method.	In both sexes, saturated fat intake increased both total cholesterol and HDL-cholesterol. Also, in both sexes, there is an inverse relationship between polyunsaturated fat intake and HDL-cholesterol. Dietary cholesterol makes no independent contribution to total serum cholesterol but increases HDL-cholesterol in women.	Adjustment through multiple regression analysis for age, height, weight, alcohol and cigarettes. Other lifestyle variables and other food components should be included in the model.
Keys 1988 (Ref. 70).	Cross-sectional re-analysis.	8829 Israeli men, 40 to 60 years.	N/A	In the original study, Israeli men were divided into 6 groups, based on region of birth. The serum cholesterol was measured only once. Keys redid the analysis of the original Israeli study, using a regression model he developed with schizophrenics.	When intra-individual variation is corrected, a highly significant relationship between mean dietary fatty acid consumption and mean serum cholesterol appears.	Keys' point that the relationship between serum cholesterol and dietary fat can not be understood by a one-time serum cholesterol measurement is well-taken. His model, which was developed in schizophrenics, has questionable representativeness. The authors from the original study have not responded.
Lowik 1991 (Ref. 83).	Cross-sectional study of dietary fats and serum cholesterol.	539 healthy elderly (aged 65 to 79y) Dutch individuals; after exclusion of those using cholesterol-lowering drugs, antidiabetic medication, and those on a dietary regimen, 199 men and 180 women remained.	N/A	Nutritional survey within the Dutch Nutrition Surveillance System; food consumption data.	Among men, intake of monounsaturated fat was positively and consistently associated with serum total cholesterol. Among women, intake of saturated fat was positively associated with serum total cholesterol.	This is a correlational study, and therefore does not look at individual outcomes. Since elderly people on a diet were excluded, those responsive to high-cholesterol diets may have been underrepresented. Confounding was well-controlled.
Mitchell 1989 (Ref. 97).	Prospective study	3301 Mexican-Americans (1393 men, 1908 women); 1877 non-Hispanic whites (835 men, 1042 women), 25 to 64 years of age.	9 years	Mean levels of cardiovascular risk factors were computed, and each subgroup was given a cardiovascular risk score. ECG's have been obtained on all subjects, and coding according to the Minnesota criteria has now been completed on all diabetic subjects.	In both men and women, triglyceride, and HDL-C was lower in Mexican-Americans than in non-Hispanic whites after controlling for age and sex, non-Hispanic white diabetics were 2.3 times as likely (no CI reported) as Mexican-American diabetics to have ECG evidence of MI.	The current risk factors might not fully capture lifetime exposure to risk factors. Current risk factors might not account for all the variance in CV outcome. Currently, only detailed information on diabetics has been compiled and analyzed; would like to see completed study on healthy individuals.

TABLE 1.—LIPIDS AND CARDIOVASCULAR DISEASE: EPIDEMIOLOGICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Test/Methods	Results	Comments and assessment
Pekkanen 1990 (Ref. 108).	Prospective study of serum lipids and CHD mortality.	2541 white men, ages 40 to 69; both free of and with a history of CVD.	10.1 years follow-up.	Baseline measurements obtained as part of the Lipids Research Clinics Program Prevalence Study, annual follow-up for mortality, not intervention. Vital status is currently known for over 99.6% of participants.	Among those with CVD at baseline, those with high TC levels (>6.19mmol/l), had a risk of death from CVD (including CHD) 3.45 times higher (95% CI 1.63 to 7.33) than those with desirable total cholesterol(TC) (<5.16 mml/l) For LDL-C: a RR of 5.92 (95% CI 2.59 to 13.51) for >4.13 mmol/l compared to <3.35 mmol/l. For HDL: a RR of 6.02 (95% CI 2.73 to 13.28) for <.90 mmol/l compared to 1.16 mmol/l. TC and LDL-C levels were also sign. predictor of death from CVD in men without preexisting CVD, but at a lower level of absolute risk of death. 10 year.	Well-controlled study. Measurements were complete; dropout rate extremely low.
Pocock 1989 (Ref. 109).	Prospective study of relationship of werum lipids to ischemic heart disease. British Regional.	7725 British men, age 40 to 59 years.	7.5 years.....	Blood samples, standardized for hr of day; morbidity and mortality documented elsewhere.	An increase in TC is associated with a significant increase in the risk of ischemic heart disease. A decrease in HDL is associated with a significant increase in the risk of ischemic heart disease. Triglycerides are not a predictor of ischemic heart disease once other factors are controlled.	Study is well-controlled
Reed 1990 (Ref. 110).	Prospective study of serum cholesetero' and CHD.	514 sets twins, male, age 42 to 55 family history of CHD, TC, HDL-C, physicians records, death certificates.	14 to 18 year.....	Used 2 way analysis of variance.	Family history of ischemic heart disease is significantly and independently correlated with ischemic heart disease. Family history is a better predictor of heart disease than blood lipids.	Well-controlled study. Data collected and analysis carried out very precisely.
Shimamoto 1989 (Ref 121).	Prospective study of the relationship of animal fat intake to CHD.	2 cohorts: 1. 2257 men and women, ages 40 to 69 at baseline, followed from 1963 to 1966 to 1973. 2. 2711 men and women, ages 40 to 69 at baseline, followed from 1972 to 1975 to 1983.	7 to 11 years.....	Surveillance through investigation all hospitalized cases plus six other ascertainment sources: national insurance claims, reports by local physicians, ambulance records, death certificates, reports by public health nurses and health volunteers, and risk factor surveys.	Animal fat intake doubled in men ages 40 to 59 from 4.5% of daily calories in 1969 to 9.6% in 1980 to 1983; significant upward shifts occurred in the means and distribution of serum total cholesterol and serum total protein in every age and sex group. Age-adjusted incidence from CHD shows no significant change overall during the 2 decades. For men and women ages 70 and older, there was no significant trend for CHD incidence except sudden death and all CHD in women, which increased significantly.	This study examines many risk factors and many outcomes (all CHD, and hemorrhagic stroke, and cerebral infarct). The nutrition survey were administered to a sample of the men. Nutritional intake was calculated by a standard Japan Food Tables. The portion of the study that relates diet to outcome uses ecologic data, which suffers from ecologic fallacy.

TABLE 1.—LIPIDS AND CARDIOVASCULAR DISEASE: EPIDEMIOLOGICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Test/Methods	Results	Comments and assessment
Slattery 1988 (Ref. 123).	Ecological comparison: CHD mortality and food consumption trends. Fat content (SA) used.	Individuals who died of CHD and dietary data during the same period.	1909 to 1980 (71 years).	Dietary data: 1. Food balance sheets. 2. Food disappearance data. 3. Household surveys from Food Agriculture Organization, Economic Research Service USDA Population data vital statistics publication.	Up to 1950 increase in CHD mortality in 45 to 54 year old and 55 to 64 year age groups. Mid 1960's to 1978 decline in CHD mortality in same age groups. Percent of total calories from fat increase from 1090 to 1960. Fats and oils contributed to 40% of total dietary fat.	Limitation on availability of accurate dietary data. Ecological data does not prove causal relationship. Latency period between change in diet and change in risk of CHD (10 to 20 year). Data did suggest a trend toward decrease in SFA and cholesterol preceded national decline in CHD.
Sprafka 1990 (Ref. 128).	Cross-sectional study of serum cholesterol and CHD mortality.	A set of Minnesota residents age 25 to 74 in 1960 to 62, and another set age 25 to 74 in 1985 to 1987.	N/A.	Analysis of covariant means and frequency distributions.	Between 1980 to 1982 and 1985 to 1987, serum total cholesterol declined significantly by 5.2mg/dl in men and 5.8 mg/dl in women. HDL decreased 1.6 mg/dl in men and 0.9 mg/dl in women. The mortality from CHD declined 20.1% in men and 12.9% in women from the 1981 survey to the 1985 one.	Multiple confounders not adjusted.
Stephen 1990 (Ref. 133).	Cross-sectional	Total US population studies included 8 to 20,000 subjects all ages, both sexes.	64 years	Results were compiled from all the studies carried out in the United States in which assessment of individual dietary intake had been carried out and where information on fat intake had been reported.	Fat intakes rise from 34% energy in the 1930's to 41% in 1960, then falling steadily to 36% energy in 1984. This trend was seen for all age and sex groups. These results differ markedly from food supply trends and indicate a fall in U.S. fat intake, which preceded the decline in heart disease mortality.	The data here is consistent with fat intake being a factor in heart disease. This study is of value to show that data gathered from food balance figures are misleading, by not allowing for waste or spoilage and includes food used for purposes other than human consumption.
Steyn 1990 (Ref. 134).	Cross-sectional study of dietary intake and serum lipids.	976 racially-mixed subjects aged 15 to 64.	Cross-sectional	Food intake was calculated from a dietary questionnaire, which included a 24-hour dietary recall. Multiple linear regression was carried out from men and women separately.	There was a significant independent correlation between serum total cholesterol and the following: dietary intake of saturated fat, intake of polyunsaturated fat, the P/S ratio, and the intake of cholesterol.	This study uses within-population data, rather than international comparison. Although this reduces the effect from genetic and environmental differences, there are still many unknown factors, which may impact upon the relationship between nutrients and total serum cholesterol.
Sytkowski 1990 (Ref. 137).	Prospective study of serum lipids and CHD.	3 male cohorts, who were 50 to 59 year old in 1950, 1960, 1970. No. subjects in each: 485, 464, 514.	Each cohort was followed for 10 year.	Risk factor assessment TC, BP, smoking, stress management.	43% reduction in 10 year risk of death from CVD in 1970 compared to 1950 group; and a 60% reduction in 10 year mortality rate in those who were free of CVD at base line. Risk factors status in 1970 and 1950 groups; from base line TC dropped 22 vs 12 mg/dl; smoking decreased 56% vs 34% and hypertension decreased from 36% vs 20%.	Well-controlled study. A decline in incidence of CVD and improved medical interventions can not be ruled out as contributing to the decline in mortality.

TABLE 1.—LIPIDS AND CARDIOVASCULAR DISEASE: EPIDEMIOLOGICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Test/Methods	Results	Comments and assessment
Trevisan 1990a (Ref. 139).	Cross-sectional study of dietary fats and serum lipids.	4903 Italian men and women, age 20 to 59 year; part of the Italian Nine Communities Study.	N/A	Interview administered PUFA and CHD risk, food frequency.	Increase in frequency of consumption of butter correlated with increase in serum cholesterol and glucose in men and with glucose in women. Olive oil and vegetable oil intake is inversely associated with serum cholesterol, glucose and systolic blood pressure	Data was adjusted for many confounders. The Italian population does not consume very much corn, or sunflower oil. This study grouped corn, soybean and sunflower oil all as PUFAs. Frequency of consumption of 53 food items, then selected top 14 of the 35 to use to calculate atherogenic index and amount (small, medium or large).
Trevisan 1990b (Ref. 140).	Cross-sectional study of diet and serum cholesterol.	10,800 men and women, ages 20 to 59, randomly selected from each of nine communities throughout Italy.	Cross-sectional	Interview-administered food frequency questionnaire.	In both sexes, serum cholesterol increased with higher consumption of foods with high fat content. These findings were independent of any possible confounding effect of age, adiposity, alcohol intake and cigarette smoking.	The detail of the food questionnaire was not sufficient to conclude that fat as a specific nutrient is responsible for the increase in the individual risk.
Van Horn 1990 (Ref. 143).	Multicenter cross-sectional study of the relation of diet to serum lipids.	5111 free-living men and women, black and white, 18 to 30 years old during the period 1985 to 1986.	1 year	Assessment interviews clinical lipids psychosocial anthropometric	Part of CARDIA Study, fat consumption significantly correlated with serum cholesterol in white men and women age 28 to 30 BMI was positively, significantly correlated with TC, LDL-C in all race and sex groups Education was positively associated with HDL-C in black and white men and women. HDL was negatively associated with carbohydrate regardless of race and sex in 25 to 30 year old group BMI was significantly, and negatively correlated with HDL in black and white men and in black women	Method of assessment of diet validated and reliable for white men and women, but not for blacks Multiple factor analysis across subgroups results in inconsistent and erroneous findings in subgroups.

TABLE 1.—LIPIDS AND CARDIOVASCULAR DISEASE: EPIDEMIOLOGICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Test Methods	Results	Comments and assessment
Yamori 1989 Ref. 146).	Cross sectional multicenter cardiac study of the relation of diet to serum lipids.	40 centers 20 countries 100 males and 100 females 50 to 54 year.	1 year	BP, clinical dietary factors CVD risk factors. Dietary: Potassium, calcium protein	Preliminary report of Cardia Study; specific regions in China have high BP, high salt intake (13 to 16 g/day), K and Ca intake low in China and Japan. Together high Na low K and Ca result in high BP and therefore increased risk for CVD Caucasia in USSR have low TC (172 mg/dl), high protein Cultural habits to boil meat which reduced fat and cholesterol, have low incidence of CVD in 7 community centers in Japan in which Na consumption in high have increased incidence of stroke and stomach cancer.	Lack of sufficient detail of dietary fat assessment; difficult to draw conclusions regarding dietary fat and heart disease

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Abbott 1990 (Ref. 2).	Diet Intervention, (lipoprotein metabolism, self controlled.	7 NonDiabetic (ND) 7 NIDDM, Pima Indians age ND 32 yr, 1 female age. NIDDM 39 (3 female cross over).	5–7 weeks diet 1: high fat, 5 wks. diet 2: low fat, high carbohydrate, 5 to 7 wks.	Solid food 1. High fat 42% of calories. 2. High Carbohydrate (65%), low fat (21%) of calories.	Consumption of high carbohydrate diet, by both ND/NIDDM groups, reduced LDL-C levels. Fractional clearance and total VLDL, LDL-C, and apoprotein B unchanged. Plasma VLDL TG increased by carbohydrate diet.	Since LDL-C was decreased in both ND/DIDDM by high carbohydrate, low fat diet; gives support for a general population strategy to lower serum cholesterol Small number of subjects. Well designed study.
Baggio 1988 (Ref. 4).	Metabolic study of impact of impact of dietary fats on serum lipids (Controlled).	11 males, 20.9 aver yr. Metabolic ward	6 week 5 week/diet	Low fat diet High fat olive oil	Found decrease in TC (−9.5%), LDL-C (−12.2%) TG (−25/5%) in olive oil enriched diet; HDL unchanged; Olive oil rich in oleic acid (C18:1). Diet compliance measured: Fatty acid; profiles of RBC membranes before and after diet; olive oil used in food. High fat diets in Mediterranean countries but low CHD death rates.	Small number of subjects, well designed and well controlled for compliance.
Berns 1990 (Ref. 5).	Dietary intervention and lifestyle study. Evaluation of diet by questionaire and diet records. Subjects divided into cohorts.	315 Dutch males 28–29 yr, free-living, selected based on BMI.	2 weeks	Representative of Dutch population; fat: 39% of calories; carbohydrate: 43% of calories, cholesterol: 128 mg/kcal.	BMI, body fat, waist/hip ratio, intra-abdominal fat and alcohol positively associated with, TC, TG Alcohol (%) strongly and independently associated with TC and HDL-C.	TC levels within population very large. Actual TC range much larger within population than predicted by Keys equation.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Berry 1991 (Ref. 6).	Randomized dietary intervention (cross-over). Evaluation of diet by diet records.	25 healthy males	12 week/diet, 32 wk study.	High MUFA diet high PUFA diet (each 32% of total calories); solid foods.	Total serum cholesterol reduced by MUFA and PUFA diets: (MUFA: 9–10%; PUFA: 16%). TG and HDL unchanged by the diets. Lipid peroxidation (measured by thiobarbituric acid reactive substance activity) increased on PUFA enriched diet. Suggested that PUFA diet could cause oxidative stress. Compliance measured by RBC membrane fatty acid composition.	Well designed and conducted study. Short duration, small number of subjects, one gender. Authors suggest MUFA not only lowers TC but may reduce atherogenic potential from oxidized LDL.
Boyd 1990 (Ref. 9).	Randomized dietary intervention.	206 women (>50 yrs of which >50% had mammographic dysplasia. Free-living	1 year	Test diet: Low fat diet decreased from 37% down to 21% of calories; carbohydrates increases from 44% up to 52% of total calories. Control diet: habitual diet	Low fat, high carbohydrate diet reduced serum cholesterol levels most in women who had the highest basal cholesterol levels. Results suggest that women and men respond similarly to low-fat diet.	Analyzed only one sample/interval. Suggested the use of serum cholesterol levels as a monitor for dietary compliance compared to estimates from food records. Results suggest women and men respond similarly to low fat diet.
Brinton 1990 (Ref. 11).	Self-controlled metabolic ward study of the effect of dietary lipids on lipoprotein and apoprotein metabolism.	13 (5 male & 8 female); Mean age: 24 yr; BMI: 22.9.	4 wk run-in; 2 diets; 4 wk per diet.	2 Diets 1. HSFA fat 42% of calories P/S 0.1. 2. LSFA fat 9% of calories P/S 1. Solid food diets, intake adjusted to maintain individual energy requirements.	Used radiolabeled apo I and II to measure FCR (fractional catabolic rate and TR (transport rate). Switch from HSFA to LSFA diet decreased HDL-C by 29% while apo AII did not change. FCR of APO I increased 11% and TR decreased 14%. FCR apo AII increased 5%. LPL decreased 23% HL decreased 17%. Increase in clearance of HDL and decrease in synthesis. Within each diet group HLD-C was inversely related to apo AI FCR but not apo AI TR. Diet influence apo AI TR which may account for decrease in HLD-C.	Diets were at extremes (42%) vs a very low fat diet (9%); diets were short term (2 wk); highly variable results; TR not measured direct but by formula which could lead to statistical artifact. Composition of baseline diet not specified.
Brown 1990 (Ref. 12).	Drug/diet intervention study, randomized, double blind.	120 men 62 year high risk CVD.	2 4 yr	1. Lovasatin (40 mg/d) + Colestipol (30 mg/d). 2. Niacin (4 mg/d) + Colestipol (30 mg/d). 3. Placebo or Colestipol.... All subjects on low-fat diet.	Serum lipid profiles and arteriographic analysis used to evaluate drug treatment-diet. Lovastatin + colestipol reduced LDL 46%, increased HDL 13%, progression of lesion limited to 21%, regression increased 32%. Niacin + colestipol reduced LDL 32%, increaed HDL 43% decreased progression 25%, regression increased to 39%. Diet reduced LDL 7% and increased HDL 5%. Aggressive drug intervention reduced incidence and frequency of MI by 73%.	Well designed study Change in CHD assessed visually and quantitatively by 2 experienced blinded observers.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Buchwald 1990 (Ref. 14).	Surgical intervention..... Randomized trial of ileal bypass surgery and serum lipids and CHD risk.	838 men/women 51 year old, high risk, MI survivors 90% men.	9.7 years.....	Ileal bypass 417 control 421 surgery.	Surgical intervention decreased TC 23%, LDL 37% and increased HDL 14.3%, decreased morbidity due to CHD (44 vs 32), reduced recurrent MI events (39 vs 24), reduced death all causes (62 vs 49). Both groups were on AHA Phase II diet.	Can not ethically have control which does not receive drug or diet to lower serum cholesterol. Good study.
Burr 1989 (Ref. 16)	Dietary intervention ..... Randomized ..... Evaluation of diet by diet questionaires.	2033 male survivors of MI; mean age 56; Wales. 4 groups; 1. reduce fat intake; 2. increase P/S ratio; 3. increase fish intake; 4. increase fibre intake	2 year.....	Experimental diets plus control. 1. Low fat (30%)..... 2. P/S of 1.0..... 3. Fish (200–400 g) per wk. 4. Fiber (cereal) 18 g/day.	No significant differences in fat or fiber group with respect to MI death, total mortality or reinfarction. Total mortality lower in fish group (29%) at 2 years, no difference in IHD events. Fiber group had slightly lower survival rate.	Differences between compliance to diets on fat and control group very small: both at about 32% fat ad 0.78 P/S ratio. TC fell 0.14 mmol/1 in low fat group (3 to 5%). Fiber compliance better. 19 g/day vs 9 g/day control group Difficult to control dietary intake.
Cobb 1991 (Ref. 18).	Drug and diet intervention. Randomized, double blind, crossover. Evaluation of diet by diet records. Metabolic ward.....	70 men/women, high risk hereditary and environmental factors.	3 wk/diet 10 day wash out.	High Fat diet vs Low Fat diet Lovastatin (40 mg/day) (drug).	Found no diet-drug synergism in reduction of blood cholesterol. Lovastatin reduced blood cholesterol on both low and high fat diets.	Did not do cross-overs, many patients were in advanced disease state, more patients (80%) had reduced cholesterol levels on low fat diet but had smaller reduction.
Cohen 1988 (Ref. 19).	Dietary intervention, effect of dietary fat on serum lipids, controlled.	12 healthy males, 20–25 yr old, exercised, non-smokers, normal glucose tolerance, non-obese.	3 days, nonfasted subjects.	Intake response: fat and blood lipids—test fat was cream [11% C14:0; 30% C16:0; 14% C18:0 and 27% C18:1]. Fat intake: 1. 40 g..... 2. 80 g..... 3. 120 g.....	Measured the effect of fat consumption on serum TG. In response: 40 g cream=251 mg/dl; 80 g cream=503 mg/dl; 120 g cream=712 mg/dl. In normal healthy males the serum TG levels were proportional to the amount of fat consumed. Maximum response to test intake was at 2 hr Test followed for 8 hr.	Well designed and executed study. Changes in serum TG varied linearly with fat content (SFA predominately) of test meal. Fat intake test within limits of how used in general population.
Curzio 1989 (Ref. 26).	Dietary intervention, randomized, free-living, diet counseling.	124 male, female 6 mo >61/gp, hypercholesterolemic hypertensive patients, age 56.5 year.	6 month.....	Low fat, high carbohydrate diet.	Compared to baseline values in 1987, both group's serum cholesterol decreased significantly. Diet intervention group decreased more in weight, TC, TG, LDL-C compared to controls. HDL-C remained unchanged.	Decrease in total cholesterol and LDL cholesterol in non-dietary group may be due to spontaneous changes in diet due to media coverage.
DeBacker 1989 (Ref. 28)	Diet, randomized..... Survey MONICA Project screening program.	134 men, 45 to 64 year, Belgium.	3 day food record.	Food consumption diary identify fatty acids, and serum lipids.	Need an objective marker to measure diet compliance within population, as well as, in individuals. Found a highly significant relationship between diet and serum CE fatty acids, but not between diet and total serum lipids.	Diet: fat 39.9%, SFA 16.6%; MUFA 14.5%, PUFA 7.1% and cholesterol 392 mg. Serum CE fatty acids: linoeate (18:2) 58%; oleate (18:1) 22%; palmitate (16:0) 13%; arachidonate (20:4) 6%.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Dreon 1990 (Ref. 37).	Diet intervention, cross-over, controlled, randomized. Diet evaluation by dietician advise and home visits.	19 males, 20 females; free-living Mormons (did not smoke, no caffeine, no alcohol, mean age 48 years)	12 wk/diet 30 wk/study 12 wk/run in.	2 Diets..... 1. PUFA enriched..... 2. MUFA enriched PUFA Saf oil MUFA O oil. Total fat 30% of calories; carbohydrate 55% of calories.	No significant change in VLDL, LDL-C, TC, HDL-C or TG due to PUFA or MUFA enriched diet. Subfraction of HDL did change HDL-2 was 50% higher and HDL-3 was slightly lower with PUFA compared to MUFA diet. APO B was 5.4% lower on PUFA diet.	Study well designed for a free living study; included eliminated many risk factor because subjects were Mormons. The authors saw no advantage of one UFA over the other with respect to total HDL-C. When subjects on low fat diet, changes in type of UFA may not alter serum-lipid levels.
Edington 1989 (Ref. 41).	Dietary intervention, crossover, free-living. Evaluation of diet by diet records.	58 men; hyperlipidemic/48 Normal chol or hyporesponders.	3 month.....	Low Fat diets 3 periods .... 1. + 410 mg chol..... 2. + 90 mg chol..... 3. + 410 mg chol	Hyperesponders = those whose plasma cholesterol increased >6%; hyporesponders + those whose plasma cholesterol increased less than 5% when diet supplemented with 3 eggs. Dietary cholesterol intake has small effect on blood cholesterol when SFA intake is low; confounders with cholesterol supplements are low SFA and high fiber.	Possible application to general population to free living and contained both hyper and hypo responder to dietary cholesterol. On low fat diet, added dietary cholesterol may not increase TC.
Frantz 1989 (Ref. 42).	Double blind, randomized trial of dietary fats, serum lipids, and CHD risk. Institutionalized ..... Single end point.....	Minnesota state mental hospitals 1 nursing home 4393 men and 4664 women.	Longest on diet 4.5 yr., mean day on diet 384, 1568 on diet > 2 yr.	Diets..... 1. High SFA + high chol.. 2. Low SFA + low chol.... Control diet= no. 1= (18% SFA, 5% PUFA, 446 mg chol); test diet no. 2 = (9% SFA, 15% PUFA, 166 mg chol).	Diets had equivalent amounts of fat but differed in SFA, MUFA and PUFA Lower SFA, high PUFA reduced TC from 203 to 175 mg/dl. No differences were observed in MI events, CVD death or total mortality when all age groups averaged. Slight increase in death (MI) in men and women on low SFA and High PUFA diets in age 45 to 55 group but not in 35 to 39 year old group.	Patients in study (81%) in hospital <1 yr, question on outside hospital compliance. Deaths from external causes higher in patients on low SFA, high MUFA, PUFA diets. Age group differences in MI and deaths.
Friday 1991 (Ref. 43).	Dietary intervention study on metabolic ward, self-controlled, cross-over.	3 men & 2 women..... Familial hypercholerolemia (FH); 5 normal aver age 40.	3 wk/diet 3 wk/washout.	3 Diets, natural foods; differ in source of FAs. 1. Butter (SFA) ..... 2. Saf oil (n-6) MUFA..... 3. Salmon oil (n-3) PUFA caloric intake adjusted to maintain individual energy requirement.	Normal subjects and similar reduction in TC, LDL-C as FH (heterozygous) patients. VLDL did not significantly change in normals but was reduced 44% in FH. PUFA diet reduced TC, LDL-C apo B slightly in FH patients compared to MUFA diet.	Very few subjects; may also have sex differences which mask final results. Both FH and normal controls, however, responded to diets (substitution of MUFA and PUFA for SFA) in similar fashion & therefore may have application to general population.
Fumeron 1991 (Ref. 44).	Diet intervention, crossover, randomized. Evaluation of diet by diet history.	36 healthy males average 23 yr.	3 wk/diet.....	2 diets..... Differ in source of FAs..... 1. 70 g Butter (SFA) 70 g control diet. 2. Sunflower oil (high PUFA) test diet.	Compared to butter diet, the sunflower oil (more PUFA) in diet reduced TC, TG, LDL-C and HDL-C. When total fat intake is high, but not excessive (even if P:S ratio is high as part of diet) there was a diminution in protective HDL and HDL-2.	Well designed study. Decrease in SFA and increasing PUFA reduced serum lipids levels (TC and LDL-C); however, also reduced HDL-C.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Ginsberg 1990 (Ref. 45).	Diet intervention, randomized, double blind, controlled. Evaluation of diet by 5 day diet record.	36 healthy, free-living, young men, 22–32 year old.	10 wk/ run in; 10 wk/ Step 1 diet; Control diet, typical American diet.	3 Diets 1. AHA Step 1 2. AHA Step 1 + 18% MUFA. 3. Amer diet AHA diet fat 30% of calories. American diet, fat 30% of calories. American diet, fat 36% of calories.	Compared two experimental diets with typical American diet effect on serum lipoprotein. Step 1 Diet reduced TC and LDL-C significantly, while TG and HLD did not change. Step 1 diet with additional MUFA (not substituted for SFA) did not significantly increase beneficial effects of Step 1 diet.	Large degree of variability in results, would have been better to use cross over design and subjects serves as own control. Carefully analyzed study. Dietary compliance stated as 85% in free living subjects, difficult to assess.
Grundy 1988a (Ref. 53).	Diet intervention; reanalysis retrospective, random.	10 to 17 men/study 4 studies patients high to normal TG and cholesterol.	6 wk/diet	4 Liquid diets 1. linoleic vs lard 2. linoleic vs palm oil 3. oleic vs palm 4. oleic vs coconut oil	Summarized 4 studies: response to SFA is highly variable. SFA was not provided from a single type of fat. Source of SFA important "If it can be shown that people with higher cholesterol levels are more responsive to SFA than those with lower levels; this would add support to the high risk strategy in causation of primary hypercholestolemia".	Small number of subjects; well designed.
Grundy 1988b (Ref. 54).	Diet intervention; metabolic ward crossover 1 month run in order diet random.	10 healthy men mean age 64 6/10 smokers.	6 wk/diet	3 Solid Food diets 1. high SFA vs high cholesterol. 2. high MUFA vs low cholesterol. 3. high carbo vs low fat	High MUFA-Low chol and low fat diet both reduced total serum chol (32 mg/dl) and LDL-C equally effectively when compared to high SFA-high col diet. Low fat diet also reduced HDL-C 6 mg/dl compared to High chol-MUFA diet. Low fat diet AHA Phase III.	Small number of subjects, smoking confounder.
Hayes 1991 (Ref. 59).	Diet intervention, crossover, random.	Non-human primates; 3 species. 8 animals /species, 10–15 yr old.	12 week per diet.	5 diets isocaloric Fat 31% of calories, diets differ in P/S ratio (range 0.1 and 1.0).	When 16:0 replaced 12:0 and 14:0 there was a significant decrease in TC and LDL-C. When 16:0 replaced 18:2 however, there was a slight increase in TC and LDL-C. 18:1 was weakly hypocholesterolemic. Plasma cholesterol in all three species affected in same direction (high P/S, lower TC) but the magnitude of the shift varied. Cebus monkey were most responsive, dropping 2.5 mmol/l TC when diet P/S ratio went from 0.12 to 1.04. Rhesus monkey was least responsive, therefore, resistant to hypercholesterolemic effect of 12:0 and 14:0.	Well designed study. Impact of any given dietary fatty acid depends upon chain length, relative saturation and relative concentration of all fatty acids available (diet, storage, part of active metabolic fats).

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Hudgins 1991 (Ref. 64).	Clinical study of trans-fatty acid intake and adipose tissue storage. randomized.	76 healthy males aver age 46.8 yr free living.	N/A	Gluteal adipose tissue fats; clinical lipids. isomeric forms of fatty acids.	Dietary *trans*-fatty acid of 18:1 and 18:2 concentrate in adipose tissue. Found no strong assoc between CVD risk factors and conc of *trans*-fatty acids in adipose. Autopsy data show however, show slight + correlation of *trans*-fatty acid with hyperlipidemia.	Careful study Possible negative correlation of consumption of *trans*-fatty acids and risk of CVD.
Johnson 1990 (Ref. 66).	Clinical trial of effect of dietary cholesterol on serum lipids. Cross-over, blinded, randomized.	10 healthy, fre living males, normal lipidemic, age 27 yr athletic	4 wk/diet	Two Diets 1. 200 mg chol 2. 600 mg chol 30% fat, 55% carbohydrate chol ' eggs natural food.	High cholesterol diet increased LDL-C and apo 8 (10 and 13% respectively) in healthy males. High cholesterol diet did not change TG, HDL-2 and HDL-3 significantly. Individual responses were highly variable. Three subjects had LDL increases >25%, 2 increased between 10-25%.	Well designed study. Small no. of subjects. importance of exercise—25 minutes aerobic exercise per day, did not prevent the cholesterol raising effect of dietary cholesterol. Dietary restriction may, therefore be justifiable even on low fat diet with exercise. Response to dietary cholesterol highly variable.
Katan 1988 (Ref. 67).	Clinical trial of effect of dietary saturated FA and cholesterol on serum lipids. Controlled, cross-over.	24/group, men and women; age 28 to 54 previously identified as hyper-responders to cholesterol:. Normal Egg eaters, Not defined what is normal egg or what HAb egg eaters consumption not defined.	3 wk/diet	Two Diets Regimens 1. Norm-Egg 21% PUFA, 11% SFA (high P/S). 2. HAB-EGG 5% PUFA, 23% SFA, (low P/S).	Question raised was do individuals who are hyperresponders to dietary cholesterol, also hyperresponders to SFA. On both diet regimens, HDL and TC increased on SFA diets and decreased on PUFA rich diets in Normal group, those who responded to increased dietary cholesterol also responded to SFA In habitual egg group, however, this was not true. Suggested that there are persons in the normal population who are both hyperresponders to dietary cholesterol and SFA Chronic egg consumption may change metabolism Dietary membranes—especially linoleic/oleic acid ratios.	Subjects in Habitual egg group were older than normal group. Small number subjects. diet short term. The authors suggest response to both dietary SFA and cholesterol congruent.
Hestin 1989 (Ref. 69).	Clinical trial of effect of fats on serum lipids. Cross-over, randomized. Evaluation of diet by dietary records and diet analysis (Each subject completed 2 diets out of 6 possible combinations).	26 healthy men average age 44.	6 week/diet	3 Fat modified Diets 1. High fat (HF)=(AUS) 2. Lacto-ovo-vegetarian (LOV). 3. Lean meat-LM	LOV and LM diets decreased BP, TC, LDL-C compared to high fat (42%) AUS diet. Both LOV and LM diets increased TG C12:0, C14:0, and C16:0 higher in AUS HF diet by minimum of 2x than LOV or LM diets. Protein source raised as possible influence on chol; wheat protein in diets LOV and LM not soy; wheat contains enriched amounts of glutamate, which may be hypocholesterolemic.	Well designed study. LM and LOV diets have similar effects on serum lipids. Compared to diet high in SFA both LM and LOV diet will reduce serum lipids. Source of protein may be important determining serum lipid levels.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Leren 1989 (Ref. 76).	Diet intervention, effect of dietary fat on CHD risk on those with and without previous MIs.	412 men, 30–64 yr who had MIs in 1956–58; half served as control Os. 1232 nonhypertensive, high risk CHD age 40–49 in 1972–73.	5, 8.5, 11 yr.	Low fat diet. Fat 39% of cal, 21% SFA, 26% MUFA, 53% PUFA. Control habitual diet. Fat 40–50% of cal., primarily SFA.	Results of secondary trial: after 5 years diet intervention group has fewer recurrent MI and fatal MI than control: Diet—43 MI/34 patients Control 64 MI/54 patients. After 11 years CHD death in Diet group was 79 and 94 in controls. In the Primary trial: measured at 5 and 8.5 years high risk CHD males which had no previous MI results showed dietary intervention reduced MI death nonfatal MI by approximately half MI death 6 diet group and 14 in control; non fatal MI 13 in diet group and 22 in control. Same trend at 8.5 years.	Estimates of recurrence of MI from secondary trial (already had MI) in those on low fat diet compared to habitual diet.
Lopes 1990 (Ref. 82).	Observational study of effects of FA intakes on serum FA. Evaluation of diet by food frequency questionnaire.	12 male/female over age 34 yr.	22 month.	Diet fatty acids compared to plasma FA in TG, PL, FFA, CE over time.	Fatty acids found in plasma in greatest abundance: 16:0-palmitic; 16:1-palmitoleic; 18:0 stearic; 18:1 oleic; 18:2-linoleic, 20:4-arachidonic. Diets vs TG–FA were most strongly correlated in men, No strong correlation between diet vs TG–FA in women; but did in FFA (18:1). Sexual difference in FA: CE:FA 20:4 male > female; PL–FA 20:4 male > female; TG–FA male 2x > than female. Fatty acid most strongly correlated with ethanol intake 16:1.	Small number of subjects and is the food frequency questionnaire adequate record of dietary intake.
Luria 1991 (Ref. 84).	Clinical study of relationship of serum lipids to extent of atherosclerosis.	380 high risk men/women average 59.	7.5 yr.	Serum lipids, and rheologic arteriographic. Pathological analysis and risk factor clustering.	Ratio TC/HDL–C closely related to presence—extent of coronary artery reduction. Divided into quartiles of highest or lowest risk. Suggested ratio is a marker for clustering of potential risk factors.	Well designed and executed study. High levels TC and low levels HDL correlated with size of coronary obstruction (reduction). An increase in the number of risk factors, the greater the risk of CVD.
Mannien 1990 (Ref. 85).	Dietary trial demonstrating effect of reduced serum lipids on CHD. Randomized, placebo control.	2590, Fredrickson Type IIa men; average age 50.	5 year.	Gemfibrozil.	Two independent variables and one is neg and one pos; difficult to predict disease outcome. Gemfibrozil raised HDL–C while lowering LDL–C. With similar LDL–C levels; those with higher HDL–C have 5x less risk of CAD. Drugs more effective against highest risk groups.	Well designed study. Medical intervention which reduces LDL–C and increase HDL–C decreases CVD risk significantly.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Manttari 1991 (Ref. 86).	Diet/drug intervention study of effect of reduced serum on apoproteins. Randomized, double blind. Evaluation of diet by diet interviews.	230 Finnish men high risk CHD half had MI during study	15 month, part of the Helsinki Heart Study.	Gemfibrozil 600 mg 2x day; placebo low fat—low chol diet all subjects. Habitual diet; fat=37-40% of total calories. Diet intervention: fat=30-35% of total calories	Subjects at baseline chosen to have similar TC and LDL-C levels, all were dysplipidemic. Out of 230 subjects 96 expressed E4 and 171 expressed E3 phenotype or in other words, 151 did not carry E4 allele. Those with dietary counseling, who expressed apo E4 allele, had the largest reduction in TC and LDL-C. For those who were treated with gemfibrozil, the same reduction in TC and LDL-C occurred with and without apo E4 allele.	Did not record SFA or cholesterol content at baseline or during the study, therefore, cannot relate specific fat with apo E regulation. Excellent laboratory analysis of apo E and possible clinical applications
Marzuki 1991 (Ref. 88).	Observational study comparing effects of two types of dietary fats on serum lipids. Residential, self-controlled, run in/wash out diets used.	110 healthy Malay males, age 16.5 year Malaysian diet.	6 wk/diet	Solid food cooked in: 1. Palm olein 2. Soybean oil fat 35% of total calories.	Regardless of cooking oil used (Palm or Soy) plasma chol and lipid profiles were unaltered Palm oil rich in 16:0 and 18:1 while Soy rich in 18:2 fatty acids.	All subjects were healthy young men, consuming native diet, with no other risk factors for CAD
McDonald 1989 (Ref. 89).	Clinical study of effects on specific fats on serum lipids. Cross-over, self-controlled. Diet evaluation by diet analysis.	8 healthy males, age 19 to 32 yr.	48 days 18 days/diet	Solid food 1. Canola (>MUFA) 2. Sunflower (>PUFA) fat 36% of calories. Canola = 59% oleic Sunflower = 73% linoleic. CanSun diet vs SunCan diet.	Canola oil rich in 18:1 while Sunflower oil rich in 18:2. Both CANSUN and SUN-CAN regiment reduced total chol; but SUN-CAN lower chol > than CAN-SUN. Neither oil altered HDL-C. Canola increased prostacyclin > than SUN. Thromboxane B-2 decreased by CAN and SUN compared to mixed fat diet CAN prolonged obstruction time.	Unlike other studies linoleic acid (18:2-SUN-PUFA) did not decrease HDL-C. Like other studies, oleic acid (MUFA) lowered TC without lowering HDL-C. Well designed study.
Mendis 1990 (Ref. 92)	Clinical study of effects of specific fats on serum lipids. Cross-over, wash out 3 wk.	25 normolipidaemic males 20-26 yr. Sri Lankan prison	8 wk/diet	Two Diets differ in P/S ratio. 1. P/S = 4 2. P/S = 0.25 Fat soya-bean and coconut oil.	Compared to baseline soya-bean diet reduced TC, LDL-C, TG and HDL significantly. Coconut diet increased TC. Normal Sri Lankan diet is 27% fat, high carbohydrate. The fat of Sri Lankan diet is primarily SFA derived from coconut oils.	Well designed and executed study. Another study that shows reduction in dietary SFA reduces TC and LDL-C.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Mensink 1989a (Ref. 93).	Clinical study of effects of specific fats on serum lipids. Randomized, controlled, diet run-in 17 days, inst food.	58 Dutch men and women 19-46 years healthy 29/gp.	36 day/test diet, 17 day run-in on high SFA diet.	Control diet: SFA 19% of energy, MUFA 11.5%; PUFA 4.6%. Test diet 1. MUFA rich, SFA 12.9%; MUFA 15.1%; PUFA 7.9%. 2. PUFA rich SFA 12.6%; MUFA 10.8%; PUFA 12.7% caloric intake adjusted to maintain energy requirements.	Compared to control diet MUFA enriched diet decreased TC and LDL-C, apo B slightly more than PUFA enriched diet in both men and women. Both test diets had lower SFA content than control diet. Test diets had a mixture of MUFA and PUFA, which in the specific test diet was enriched. Both test diets reduced HDL-C (PUFA>MUFA) was more in men than women.	Compliance determined by fatty acid content in serum CE. Individuals on MUFA diet had more oleic acid in CE and those on PUFA had more linoleic in CE. MUFA enriched diet as effective or better than PUFA enriched diet in lowering serum cholesterol. Several subject had influenza like symptoms concomitantly with decreased HDL-C. Well designed and executed study.
Mensink 1989b (Ref. 94).	Clinical study of effects of specific fats on serum lipids. Diet run-in, controlled	48 healthy adult men/women, Dutch and 76, 8 to 10 years old Cretes.	36 day/test diet 17 day run in on high SFA diet.	Diets 1. Control diet high SFA 20%, 38% total fat; 47% Carbo. 2. High Carbo 62%; low fat 22%; SFA 6.7%. 3. Olive oil fat 40.6%, SFA 9.8%, MUFA 24% carbo 46%.	Results from clinical study compared to Crete boys diet and serum lipids. Dutch study: TC decreased 0.44 mmol/1 on high carbohydrate diet and 0.46 mmol/1 on olive oil diet HDL-C fell on high carbohydrate diet 0.19 mmol/1 and increased on olive oil diet (0.03 mmol/1). Epi study and clinical study did not agree on effect of olive oil diet on serum lipids.	Compared 8 to 10 year old boys in Crete with adult men/women in Holland. Used pooled blood samples to analyze lipoprotein profile in Crete boys. Food intake examined on two consecutive days. Study tried to compare to many subgroups and cross study design types. Compares apples and oranges.
Mensink 1990 (Ref. 95).	Clinical study of effect of specific fats on serum lipids Cross-over, randomized, controlled, no wash out.	34 women 25 men average age 25 healthy 8 women on oral contraceptives.	3 week/diet	3 Diets Diets differ fatty acids (10%). 1. oleic, cis 2. elaidic, trans 3. SFA, 12:0, 16:0	Diet were identical, varied only 10% fatty acid as either. 1. oleic, cis; 2. elaidic trans or 3. SFA lauric and palmitic. Compared to oleic acid, *trans* form increased LDL-C significantly (14 mg/dl) and decreased HDL-C by 7 mg/dl. SFA increased LDL-C (18 mg/dl) but HDL-C was unchanged.	Excellent well designed and executed study, well controlled. *Trans*-F.A. could increase risk CVD at higher levels than currently consumed. *Trans*-fatty acid not only raised LDL-C but lowered HDL-C as well. The concentration of *trans*-fatty acid used was higher than current availability data in US population.
Miettinen 1989 (Ref. 96).	Clinical of effect of dietary cholesterol on cholesterol metabolism. Cohort evaluation of clinical results with dietary intake, randomized diet. Evaluation of diet by dietary records.	63, 51 year old males, normal, free living, random selection.	>1 week	0.14, uCi Chol; 0.28, uCi B-Sitosterol; 200 mg Cr203. Cholesterol: 487 mg/day Fat: 108 g/day Habitual diet	Cholesterol absorption efficiency reduced by obesity. Absorption of dietary chol increased with intake. The more fractional and absolute chol absorbed; the more chol synthesis inhibited. 1 mg.kg/day chol=decrease 2.2 mg.kg/day of chol synthesis. The higher the synthesis of biliary chol the lower the absorption of dietary chol. Plant sterol reduced fractional chol absorption; enhanced fecal chol elimination.	Well designed study. The authors conclude that the amount of chol absorbed may regulate both chol synthesis and elimination in some individuals more than others.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
MRFIT Research Group 1990 (Ref. 101).	Community trial of diet and lifestyle intervention on serum lipids and CHD risk. Randomized, controlled. Special Intervention (SI).	12,866 CHD high risk men, 35 to 57 years.	10.4 years	SI..... 1. Diet low fat, chol..... 2. Smoking..... 3. Drug for hypertension...	Intervention group had lower mortality at 10.5 yrs from all causes (−7.75), CHD (−10.6%) and CVD (−8.3%). There was a 24% reduction in death due to acute MI in special intervention (SI) group. Risk factors for CHD declined in both groups. SI group had increase in death related to respiratory and intrathoracic organs (+20.1) and digestive system (+36.8%). Used blood pressure reducing drug: chlorthalidone and hydrochlorothiazide.	Well designed and executed study. The more risk factors reduced, the greater reduction of CVD risk.
Nervi 1989 (Ref. 102).	Clinical study of effect of high carbohydrate diet on serum lipids and gallstones. Institutional food consumed 6 days/week.	20 (18–22 year) healthy men Chilean.	1 month/diet.....	Two diet regiments..... 120 g/day legumes vs isocaloric no legumes.	Legume diet compared to control diet: decreased LDL-C, HDL-C, increased biliary cholesterol saturation in 19 out of 20 subjects by at least 50%. Legume consumption suggested as a risk factor for cholesterol gallstone. Biliary total lipids concentration same however, PL concentration down and cholesterol and bile salts up.	Well designed and executed study. An 8% amino acid solution was used to stimulate gallbladder contraction; different legumes used have variable concentration of possible active components, such as saponin.
Ng 1991 (Ref. 103).	Clinical trial of effect of types of FAs on serum lips. Randomized, cross-over, double blind. Evaluation of diet by diet records (food provided).	123, Malay men (61) and women, age 24 random assigned to 3 test groups.	5 wk/ test diet.... 15 wk/study.....	3 diet regiments..... 1. Coco-palm-coco..... 2. Coco-corn-coco ..... 3. Coconut solid food cooked in oils.	Diet fat was 32% of total calories. The oil provided 75% of the total fat. Coconut oil raised chol 10%. Palm olein and corn oil reduced chol (−19 and 36%), reduced LDL-C ad HDL-C. Corn oil reduced TC, LDL-C and HDL-C more than palm olein. Corn oil hypotriglyceridemic.	Over simplification to judge an oil solely on basis of SFA content. No dietary baseline data provided, actual intakes, changes in body wt, adjustment for confounders not reported.
O'Dea 1990 (Ref. 105).	Clinical study of effect of dietary fats on serum lipids. Controlled..... Evaluation of diet by diet records.	10 healthy men/women, average 25.2 yr.	5 wk/study run in 1 wk.	Very low fat [fat-lean meat] vs added beef fat to very low fat = 8% high fat = 20–30%.	Within 1 week on extreme low fat diet, total chol dropped 9%, LDL-C dropped significantly and HDL-C dropped but not significantly TG increased significantly on low fat diet. Beef fat, not beef meat, identified as dietary risk factor in raising blood chol. Beef fat 20 and 30% of total calories raised blood cholesterol. The higher the P:S ratio the more the HDL falls along with LDL-C. Diets, not excessively low in SFA nor increasing in PUFA do not generally raise HDL-C levels.	Small number of subjects. Short run in for diet. Study results indicate that it is the fat from beef that increases serum cholesterol and not the beef.

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/test/dose	Results	Assessment/comments
Ornish 199 (Ref. 106).	Clinical trial of effect of diet and lifestyle on serum lipids and atherosclerosis. Prospective, controlled.	48 high risk CHD, free-living men, 5 women; age 56 year (expt) 50 year (control) have atherosclerosis. Coronary arteries assessed at baseline and after 1 yr.	1 year	Diet Intervention. 1. Low fat veg diet non-smoking stress management moderate exercise. 2. Usual Care	Short term life style intervention (1 year) reduced the diameter of the stenosis in patients with atherosclerosis and appeared to reduce the progression of the disease. TC, LDL-C reduced, HDL-C unchanged, TG elevated in intervention group. Fat intake reduced to 6.8% of total calories in intervention group compared to 30% in cholesterol.	Well designed and executed study. Results suggest that low fat, vegetarian diet reduced the profession (or regression) of atherosclerotic plaque.
Rifail 193 (Ref. 111).	Clinical study of effect of amounts of fat in test meal on serum lipids. Method(s) compared to calculated values.	16, healthy males, 23–34 yr non smokers postprandial effects.	8 hour	High fat test meal, 70 gm fat, 580 mg chol, 1110 calories: 56% fat.	A single high fat meal increased TG and VLDL. Maximum response to test meal at 3 hr HDL's Apo A's and apo B were not altered by fat meal by 8 hr. Differences between measured directly (LRC Method) versus. Calculated values by Friedwald equation. If patient not fasted, the LDL-C concentration will be significantly underestimate. To minimize postprandial effect on plasma lipoprotein, a minimum of 8 hr fat is required for accurate measurement of VLDL. TC, HDL's, apo A and B can be determined adequately using non fasting serum.	Short time, small number subjects. Results should be considered when cross comparing design and results from different laboratories.
Sorci-Thomas 1989 (Ref. 127).	Animal study of effect of diet on serum lipids. Mechanism, dietary intervention.	25 adult male African green monkeys.	1 year, 5 yr form most animals (male).	4 Diet Regiments Low Chol + high PUFA. Low Chol + Low PUFA. High Chol + high PUFA. Low Chol + Low PUFA. Chol 0.03 or 0.8 mg/kcal P/S ratio, 0.3 or 2.2.	Diet high in chol., generally increased TC, LDL-C and apo B. PUFA enriched diet reduced TC, HDL-C and plasma apo A-1 in monkeys fed high choiesterol diet by 13, 28 and 16% respectively. PUFA also decreased rate of A-1 production in the liver but not in the intestine. Effect of PUFA on apo A-1 synthesis was tissue specific.	Well designed and executed study. Monkeys respond to dietary changes in a manner similar to humans. Dietary effect of PUFA on synthesis of CHD protective factor. PUFA reduced the synthesis of apo A-1 and therefore could increase CHD risk (mechanism).
Ikkanen 1990 (Ref. 139).	Clinical trial of amount and type of dietary fats on serum lipids and apoproteins. Dietary intervention apo E phenotype.	110 North Karelian (Finland) 30–50 y.o. 56 men and 54 women healthy fresh blood.	6 wk/diet, and 12 wk/diet, with 5 wk/ switch back.	Test diet. Diet 1. Low fat, P/S = 1. Diet 2. Low fat low salt, P/S 0.4. Baseline diet, high SFA high chol.	Plasma chol correlated inversely with apo E 3/4 isoforms. Highest plasma chol found in apo E4/4. Subjects with apo E3/2 has lowest plasma chol. Association weaker on low fat , low chol diet. Greatest reduction in TC in apo E4/4. When diet switched back, these subjects had highest increase in TC.	Excellent study; The apo E phenotype may in part, determine the amount or response to dietary fat and chol which results in alteration of serum lipids levels. An apo E allele sum of 7 or more are greatest risk and most responsive to dietary lipids (mechanism).

TABLE 2.—LIPIDS AND CARDIOVASCULAR DISEASE: CLINICAL STUDIES (SCIENCE SUMMARY UPDATE)—Continued

Reference	Study design	Study population	Duration	Method/Test/dose	Results	Assessment/comments
Wardlaw 1990 (Ref. 144).	Clinical study of effect of types of dietary fat on serum lipids. Double blinded, randomized, cross-over.	20 men, average 34.7 yr normal diet fat 37–43% calories	5 week diet phase; 7 wk/ washout; cross-over and repeat.	Diets..... 1. Butter—2 wk..... 2. Corn-PUFA..... 3. Sun-MUFA.....	Both vegetable oil diets (PUFA and MUFA) reduced chol 16–21%, LDL-C 21–26% and TG by 10–21% compared to butter diet. Serum chol falls within 1 wk on vegetable oil diets. Dietary chol raised from 190 to 500 mg/day while on vegetable oil diet did not change serum TC, LDL-C, HDL-C or TG. High Concentration of PUFA may have pharmacological effects on lowering HDL-C, however, diets containing 35% of calories from fat and P-S ratio < 1.5 are not likely to lower HDL significantly.	Well designed and executed study. Applicable to men who consume high SFA diet (did not include women). Consumption of low fat diet reduced serum lipids levels in young healthy men who had previously consumed high fat diet. Furthermore the authors suggest some risk may be involved as reduce SFA in diet, especially substitute PUFA for MUFA.
Wood 1991 (Ref. 145).	Clinical study of effect of diet and exercise on serum lipids. Randomized, controlled. Evaluation of diet and activity by clinical activity logs, 7 day diet records, and telephone interviews.	Moderately overweight, sedentary men and women (132 each), 25 to 49 yr old; 119 men & 112 women completed study; non-smokers, low alcoholic consumption.	1 year.....	Divided into 3 cohorts 44 men & 44 women in each cohort. 1. Control, habitual diet..... 2. Hypocaloric NCEP diet 3. Hypocaloric NCEP diet (+) exercise.	Both NCEP groups reduced body fat significantly and BP. In men: Diet (+) exercise increased HDL, while decreasing TG, apo B HDL increased significantly (13%) in men who exercised over diet alone. In women: Diet alone & (+) exercise significantly reduced BP, TC, apo B compared to controls. Women in diet alone group, had significantly lower HDL-2 and apo A-1 compared to control. Addition of exercise decreased the reduction of HDL-2 by low fat diet.	Well designed and well executed study. Suggests multifactorial approach for reduction CVD. Exercise is important in increasing level HDL. Diet is important in reduction of TC and LDL-C.

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21 CFR Part 101

[Docket No. 91N-0097]

RIN 0905-AD08

Food Labeling: Health Messages; Dietary Lipids and Cancer

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to authorize health claims on foods and food labeling that state that diets low in total fat may reduce the risk of some types of cancer, particularly colon, breast, and prostate, in the general population. The agency reviewed this topic under the provisions of the Nutrition Labeling and Education Act of 1990. The agency's conclusion is based on its review of the publicly available scientific literature. The strength and consistency of the scientific data supports such claims. Under this proposal, it also may not imply any particular degree of risk reduction. The proposed rule requires that to bear such a claim, the food or food product must meet the criteria proposed in § 101.62 for a "low fat" claim. FDA is proposing to permit foods that qualify to use a combined cancer-cardiovascular disease label statement and is requesting comments addressing scientific and compliance issues that may arise from the use of such combined health claims.

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

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: He-Chong C. Lee, Center for Food Safety and Applied Nutrition (HFF-265), Food and Drug Administration, 200 C St. SW Washington, DC 20204, 202-485-0358.