DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 91N-0096]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements; Dietary Saturated Fat and Cholesterol and Coronary Heart Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing its decision to authorize the use on the label or labeling of certain foods of health claims relating to an association between dietary lipids (specifically, saturated fat and cholesterol) and cardiovascular disease (specifically, coronary heart disease (CHD)). The agency has concluded that, based on the totality of the scientific evidence, there is significant scientific agreement among qualified experts that diets low in saturated fat and cholesterol may reduce the risk of heart disease. Therefore, FDA has concluded that claims on foods relating the reduction in dietary saturated fat and cholesterol to reduced risk of CHD are justified. This action is in response to provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) that bear on health claims and has been developed in accordance with the final rule on general requirements for health claims, which is published elsewhere in this issue of the Federal Register.

EFFECTIVE DATE: May 8, 1993.

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 27, 1991 (56 FR 60727), FDA proposed to authorize the use in food labeling of health claims relating diets low in saturated fat and cholesterol to decreased risk of CHD. The proposed rule was issued in response to provisions of the 1990 amendments (Pub. L. 101-535) that bear on health claims and in accordance with the proposed general requirements for health claims for food (56 FR 60537, November 27, 1991). As amended by the 1990 amendments, the Federal Food, Drug, and Cosmetic Act (the act) provides that a food is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition unless the claim is made in accordance with section 403(r)(3) or (r)(5)(D) of the act (21 U.S.C. 343(r)(3) or (r)(5)(D)).

Section 3(b)(1)(A) of the 1990 amendments specifically requires that the agency determine whether claims respecting 10 nutrient/disease relationships meet the requirements of section 403(r)(3) or (r)(5)(D) of the act. The relationship between dietary lipids and cardiovascular disease is one of the claims required to be evaluated. In the **Federal Register** of March 28, 1991 (56 FR 12932), FDA published a notice requesting scientific data and information on the 10 specific topic areas identified. Relevant scientific studies and data received in response to this request were considered as part of the agency's review of the scientific literature on lipids and cardiovascular disease. Comments received in response to the notice and not specifically addressed in the proposed rule are summarized and addressed in this document.

Because of the extremely large volume of scientific literature on this topic, FDA limited its scientific review to those aspects of the relationship for which the strongest scientific evidence and agreement already existed: dietary intakes of total saturated fats and cholesterol relative to risk of CHD. In addition to evaluating the scientific evidence relating saturated fat and cholesterol to cardiovascular disease, the proposed rule identified qualifying and disqualifying criteria for foods, specified mandatory and optional information for health claims statements, and provided model health claims. FDA also discussed potential safety issues associated with reducing current dietary intakes of saturated fat, cholesterol, and total fat.

FDA requested written comments in response to the proposed rule and solicited comments on several issues in particular. The agency asked how to restrict the use of these health claims to foods that are appropriately included as part of healthy diets, and whether .there. is a need for consumer summaries.

On January 30 and 31, 1992, FDA held public hearings on all aspects of the proposed rules published in response to the 1990 amendments, including health claims for dietary saturated fat and cholesterol and heart disease (57 FR 239).

In response to its proposed health claim on lipids and cardiovascular disease, the agency received approximately 100 comments from consumers, consumer advocacy groups, State health departments, organizations of health professionals, the food industry, and Government agencies. A number of comments were received that were more appropriately answered in other documents, and these were forwarded to the appropriate docket for response.

II. Comments on the Relationship Between Dietary Saturated Fats and Cholesterol and CHD

The majority of comments supported FDA's conclusion, noting that the scientific evidence that dietary saturated fat and cholesterol increase the risk of CHD is very strong and well accepted in the scientific community. Many of these comments provided little or no detail on their reasoning. One detailed comment that supported the saturated fat and cholesterol/heart disease relationship was the report of the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB), which evaluated recent scientific publications on this topic. The FASEB draft report was summarized by FDA in the November 27, 1991, proposal (Ref. 78). The final report was submitted to the docket as a comment (Ref. 196). The conclusions of the final LSRO report concur with previous dietary guideline recommendations that reducing intakes of saturated fat and cholesterol would lower total blood and low-density lipoprotein-cholesterol (LDL-cholesterol) levels and, thus, lower risks of CHD in the U.S. population.

A number of comments suggested Modification and revision in various provisions of the proposal. A summary of the suggested changes and the agency's responses follows.

1. The agency received a number of comments focusing exclusively on dietary cholesterol as a risk factor for heart disease. Some comments suggested that the scientific evidence does not support a relationship between dietary cholesterol and blood cholesterol levels and suggested that the nutrient/disease linkage is primarily with saturated fat. The comments noted that most dietary cholesterol is not absorbed, and that individual responses to dietary cholesterol are highly variable. Conversely, many comments noted the compelling nature of the scientific evidence linking dietary cholesterol to risk of heart disease. The 1992 LSRO review of the science on this topic (Ref. 196) not only strongly supported the relationship between dietary cholesterol and increased blood

cholesterol levels but suggested that newer evidence increased the importance of dietary cholesterol as a risk factor for heart disease.

FDA agrees with those comments that suggested that there is adequate scientific evidence and significant scientific agreement that diets high in cholesterol increase the risk of heart disease. This conclusion is consistent with current dietary guidance and nutrition policy statements from the Federal Government (Refs. 29, 36, 136, and 150), the National Academy of Sciences (Ref. 20), and the recent LSRO report (Ref. 196). None of the comments that argued against such a link submitted either data or compelling logic to convince FDA that this conclusion is not correct. FDA recognize that there is some scientific disagreement about the relative importance of dietary cholesterol versus saturated fat intakes (56 FR 60730). However, there are strong and consistent data that support that saturated fat and cholesterol have independent effects on the risk of heart disease. Because the data support an independent effect for dietary cholesterol and for saturated fat, the relative importance of dietary cholesterol versus saturated fat on blood cholesterol levels and risk of heart disease really is irrelevant to the agency's conclusion that a health claim on both nutrients is appropriate. FDA recognizes that individual responses to dietary cholesterol are less consistent than to saturated fat. However, recent authoritative reviews (Refs. 20, 29, 31 through 36, 63, 71, 74, 98, 99, 129, 130, 136, 141, 150, 151, and 223) have concluded that the majority of persons in the United States will benefit from recommended dietary changes in cholesterol intake, even though the magnitude of the benefit varies among individuals.

2. Several comments stated that FDA did not address the issue of a beneficial role for dietary *cis*-monounsaturated fatty acids (MUFA's), a major source of dietary fat in the United States, in reducing the risk of heart disease. In this context, one comment noted that the Keys equation, which was used in several studies for predicting or explaining changes in blood total cholesterol based on dietary intakes of saturated and polyunsaturated fatty acids (PUFA's), was inadequate as a basis for evaluating the role of dietary lipids in reducing risk of heart disease, because it does not include a term for the amount of MUFA's. The comment further stated that, in light of newer data on possible beneficial effects of MUFA's, this equation may no longer adequately reflect the predictive value of changes in fat intakes to changes in blood cholesterol levels in the U.S. population.

The LSRO report (Ref. 196) evaluated the potential usefulness of oleic acid, the major *cis*-monounsaturated fatty acid, as a replacement for saturated fat in the American diet. The report concluded that recent research results are consistent with the conclusions that substitution of oleic acid for saturated fatty acids (SFA's) in the diet is safe and without adverse effects on blood LDL-cholesterol levels. The report stated that substitution of *cis*-monounsaturated fats for saturated fats can allow Americans to maintain customary intakes of total dietary fat without the negative effects of the more cholesterol-raising SFA's (i.e., lauric, myristic, and palmitic fatty acids). The LSRO report noted, however, that a diet high in monounsaturated fats (i.e., oleic acid) may contribute to development of obesity, a risk factor for heart disease.

FDA is aware of the recent and ongoing research efforts on the possible beneficial role of *cis*-forms of MUFA's in helping Americans to find a practical means of reducing saturated fat intake without changing total dietary fat intakes (Refs. 6, 37, 53, 57, 89, 93, 139, 144, 158, 159, 175, 180, 188, 192, 196, and 219). FDA, however, considers this issue outside the scope of this rule. In the proposed rule, the agency noted that, because of the extremely large volume of scientific research on lipids and cardiovascular disease and because of the extremely limited time constraints of the 1990 amendments, it had limited its science review to an evaluation of the relationship of saturated fat and cholesterol intakes to risk of CHD. Therefore, in both the proposed and final rules, FDA has limited the health claim to saturated fats and cholesterol.

FDA notes that the rapidly expanding science base may now, or in the future, be adequate to support that *cis*-monounsaturated fatty acids have a beneficial role in reducing blood total and LDL-cholesterol levels. However, because the question of whether this nutrient/disease relationship is appropriate for a health claim is outside the scope of this rulemaking, the question should be the subject of a petition for a health claim in accordance with the provisions of the final rule on general requirements for health claims published elsewhere in this issue of the **Federal Register**.

3. One comment suggested that novel fats that affect a surrogate marker for the disease, Such as lowering of blood LDL-cholesterol, should be allowed to carry a health claim.

FDA is aware that a large amount of research and development is being done on novel fats. Novel fats are those fats that are not commonly found in the food supply. Some examples of novel fats include those fats modified by rearrangement of fatty acids in triglyceride or by the addition of a cyclic or aromatic ring to a fatty acid. (The issue of "bioavailability" of novel fats is addressed elsewhere in this issue of the **Federal Register** in the final rules on mandatory nutrition labeling, nutrient content claims, and health claims.)

FDA did not have any scientific evidence on the possible effects of specific novel fats on risk of heart disease, or on other validated surrogate markers for heart disease, in developing this final rule. Therefore, FDA has not dealt with this issue in this final rule.

III. Qualifying Nutrients

The qualifying levels for saturated fat, cholesterol, and total fat are the maximum level at which these nutrients may be present in a food if it is to qualify to bear a claim. The levels of saturated fat, cholesterol, and total fat in a food must be less than those specified in the qualifying levels for the food to be eligible.

A. Saturated Fat and Cholesterol

In the proposed rule, FDA tentatively provided that, to bear a claim associating a diet low in saturated fat and cholesterol with reduced rate of coronary heart disease, the food must be "low saturated fat," "low cholesterol," and "low fat," as those terms are defined in new § 101.62. FDA also proposed to require that the food contain 1 g or less of saturated fat per 100 got food.

4. A number of comments recommended that claims include information about the amount of saturated fat and cholesterol beyond the information contained on the nutrition panel. Some comments recommended the use of an index or "cholesterol-saturated fat index" (CSI) that integrates known relative effects of saturated fat and cholesterol intakes in predicting increased changes in total and LDL-cholesterol levels (Refs. 202 and 203). These comments pointed out that the CSI consists of a single score or number by which it would be possible to determine the relative cholesterol-raising propensity of a given food. The comments suggested that the CSI for a given food would be calculated from the experimentally-derived formula: (1.01 x g saturated fat) + (0.05 x mg cholesterol).

One comment included a detailed listing of CSI's for a wide variety of foods, including milk with 1-percent fat, which had a CSI of 2, and butter, which had a CSI of 37.

FDA agrees with the concept that consumers should have label information presented in a manner that enables them to evaluate an individual food relative to total dietary goals. However, the agency has not included any requirement for use of a CSI index in the final rule. The comments did not provide data to show that consumers would find use of a CSI index more helpful than the nutrition information currently required on food labeling. FDA is concerned that consumers might place undue emphasis on the CSI index in purchasing decisions and not concentrate on consuming healthful diets, which include a variety of foods.

FDA considers that a consistent approach to nutrition information on food labels will be less confusing to consumers than the use of a CSI index. FDA's general approach is to provide information that allows a consumer to construct a diet that is consistent with the particular health claim and with general dietary recommendations. The use of a CSI index, however, would be inconsistent with that approach because it would likely lead the consumer to place more emphasis on the specific food than on the entire diet. In addition, the larger scientific community has not generally agreed on a particular symbol or approach, such as the CSI index, for helping consumers to identify foods that will help lower their risk of heart disease.

Thus, FDA is retaining its proposed approach with respect to the label information that must appear on foods that qualify for a health claim on lipids and heart disease.

5. A few comments suggested that foods that contain eggs or egg products should be eligible to bear the authorized health claim.

The agency agrees that a food containing eggs or egg products should not be denied a health claim for saturated fat and cholesterol and heart disease, provided that the food is "low saturated fat," "low cholesterol," and "low total fat" and meets the other qualifying requirements for a health claim on this topic. The qualifying criterion for cholesterol is based on the final concentration of cholesterol in the food product and not on the cholesterol content of ingredients. Therefore, if eggs and egg products used as ingredients do not cause a food to exceed the definition of "low cholesterol," the food may qualify for a health claim.

6. Other comments suggested that the qualifying level for the saturated fat and cholesterol content of a serving of food be made less restrictive so that a larger number of wholesome foods can qualify for a health claim. Some of the comments stated that the permissible level of 1 g of saturated fat for a serving of food should be increased to 2 g. A few comments proposed that "foods that contain 20 milligrams or less of cholesterol per serving and 2 grams or less of saturated fat should be allowed to make a health claim." Other comments asserted that the saturated fat and cholesterol/heart disease health claims should be allowed on foods that qualify for the comparative claim, "reduced cholesterol." Some comments also objected to the per 100 g density criterion for qualifying levels of saturated fat and cholesterol, suggesting that it unfairly discriminates against foods that have a useful dietary role in reducing the risk of heart disease but that, because their servings sizes are less than 100 g, exceed the qualifying criterion on a per 100-g density basis.

Based on the large number of comments that the agency received, FDA has reassessed the qualifying levels for saturated fat. total fat, and cholesterol, including the density criterion. (See the final rule on general requirements for nutrient content claims published in this issue of the **Federal Register** for a more detailed discussion. FDA incorporates that discussion by cross reference. Based on this reanalysis and on the comments received, FDA has been persuaded that the second qualifying criterion based on per 100 g is too restrictive for "low fat" and "low cholesterol" claims. (The proposed definition for "low cholesterol" did not include a per 100-g criterion.) The agency has concluded that this criterion should be modified to more directly reflect the nutrient dense foods with small serving sizes that it was designed to address. Therefore, FDA has modified the density Criterion from a per 100-g basis to a per 50-g basis for foods that have a reference amount customarily consumed of 30 g or of 2 tablespoons or less. With this modification, a larger number of wholesome foods may qualify for a health claim, including more brands of breakfast cereals and cereal grain products (Ref. 222).

The agency disagrees that "reduced cholesterol" and other comparative claims should be the basis for qualifying levels of nutrients. Many foods, even after meeting the requirements for "reduced" claims, contain significant amounts of saturated fat or cholesterol. When making substitute choices among similar types of foods (e.g., deciding upon which brand of vegetable oil to purchase), comparison claims are very useful in helping consumers to make a choice. However, when putting foods together within a total dietary context, the absolute amount of nutrient present in a food is important.

7. Some comments noted that FDA's proposed definition of saturated fat (i.e., the sum of lauric, myristic, palmitic, and stearic acids) is not consistent with the most recent evidence on cholesterol-raising fatty acids. The comments suggested that the cholesterol-raising characteristics of SFA'S are due almost entirely to three SFA's: lauric, myristic and palmitic fatty acids. Conversely, stearic acid, which is a significant source of SFA'S in the U.S. diet, has relatively little effect on blood cholesterol levels. The comments further note that this variability in cholesterol-raising potential opens new opportunities to replace cholesterol-raising saturates with other saturates that are not cholesterol-raisers (i.e., stearic acid).

The agency agrees that specific SFA'S vary in their potential for an adverse effect on blood cholesterol levels and on other atherosclerotic risk factors. In the proposed rule (56 FR 60727 at 60734), FDA acknowledged that lauric, myristic, and palmitic SFA'S have the greatest effect on blood cholesterol levels, and that, in this respect, stearic acid is relatively neutral. FDA disagrees, however, that the definition of saturated fat should be limited only to the sum of lauric, myristic, and palmitic fatty acids. In the final rule on mandatory nutrition labeling published elsewhere in this issue of the **Federal Register**, and in response to comments, FDA has changed the definition of saturated fat to include the sum of all fatty acids containing no double bonds. This definition will apply to all references to saturated fat on the food label. Also, as noted in the preamble to the final rule on mandatory nutrition labeling published elsewhere in this issue of the **Federal Register**, this definition for saturated fat is consistent with dietary guidelines for diets to reduce risk of heart disease (i.e., consume less than 10 percent of calories as saturated fat; therefore, all four saturated fat (lauric, myristic, palmitic and stearic) plus less abundant saturated fats are included in the new definition.) Furthermore, FDA has noted that elevated blood cholesterol is not the only risk factor for cardiovascular disease (56 FR 60727 at 60734). Saturated fats have been implicated as possibly increasing the risk of cardiovascular disease through mechanisms other than adverse effects

on blood total and LDL-cholesterol (Ref. 20).

B. Total Dietary Fat as a Qualifying Criterion

In the proposal (56 FR 60727 at 60739), FDA proposed to prohibit health claims relating, diets low in saturated fat or cholesterol to lower blood cholesterol levels and reduced risk of CHD unless the food also meets requirements for a "low" claim relative to total fat content (i.e., 3 g or less of fat per label serving size, per reference amount customarily consumed, and per 100 g). FDA notes that, while total fat is not as strongly or directly linked to increased risk of CHD as it may have significant indirect effects.

8. A number of comments supported the agency's position that a food must not only be low in saturated fat and low in cholesterol but must also be low in total fat, and that decreasing total fat intakes will generally aid in decreasing intakes of saturated fat and cholesterol. However, several comments opposed the additional "low fat" qualifying criterion, suggesting that foods recommended by public health authorities (such as fish, chicken, and lean beef and vegetable oils that are low in saturated fat and cholesterol) would not qualify, for a health claim and that this would appear inconsistent with efforts to encourage an overall healthful diet.

FDA agrees that total fats are an appropriate qualifying criterion, and this provision is retained in new § 101.75(c)(2)(ii). (In the November 1991 proposed rules, FDA combined the regulations for lipids and cardiovascular disease (proposed § 101.73(a)) and lipids and cancer (proposed § 101.73(b)) into one section. In these final regulations, FDA has separated the two health claims into individual sections. New § 101.75 covers dietary saturated fat and cholesterol and coronary heart disease. New § 101.73 covers dietary fat and cancer.) FDA has retained this criterion because low fat foods generally help individuals in reducing their intake of saturated fat and cholesterol. In addition, excess calories, of which fat contributes more per g than the other energy nutrients, is associated with two health-related conditions (obesity and diabetes) that are risk factors for heart disease. These provisions now read in new § 101.75(c)(2)(ii): "The food shall meet all the requirements for a 'low saturated fat,' 'low cholesterol,' and 'low fat' food;* * *."

FDA agrees that lean meats, fish, and poultry, when eaten in moderation and prepared with little or no added fat, can play an important role in helping consumers to meet dietary guidelines. Meats, fish, and poultry play an important role in the U.S. dietary pattern, serving as entrees as well as rich sources of protein, bioavailable sources of many minerals, and rich sources of several vitamins. As proposed, the qualifying criteria virtually prohibit this category of foods from bearing health claims. As a result, the proposed criteria may inadvertantly interfere with the-dietary guidance goals of encouraging consumption of a variety of foods and of increased use of lean meats, fish, and poultry instead of higher fat cuts.

In the final rule on general requirements for nutrient content claims published elsewhere in this issue of the **Federal Register**, FDA is defining the term "extra lean" as a claim for game meats and fish. Although this definition is not as stringent as the definition for "low fat," "'low saturated fat," and "low-cholesterol," it is consistent with the U.S. Department of Agriculture (USDA) definition for "extra lean" for meats and poultry.

The agency is persuaded that, to be consistent with the dietary guidance goals discussed above, health claims should be allowed on "extra lean" cuts of meat, fish, and poultry. FDA is therefore providing for saturated fat and cholesterol/CHD claims on "extra lean" game meats and fish that meet these requirements. This provision is added in new § 101.75(c)(2)(ii) which reads: "* * * except that fish and game meats (i.e., deer, bison, rabbit, quail, geese, and ostrich), may meet the requirements for 'extra lean' in §101.62."

FDA disagrees with the comment suggesting that foods consisting entirely of fats and oils, but low in saturated fat and cholesterol, should qualify for heart disease health claims. Low fat diets are recommended in all Federal Government and National Academy of Sciences' dietary guidelines for reducing the risk of heart disease. Labeling of foods that are 100-percent fat with a message implying they are "heart healthy" is clearly inconsistent with dietary guidelines, FDA believes that the use of content claims is a more appropriate method for helping consumers make purchasing decisions about those oil products that they choose to include in their total daily diet than allowing those foods to bear health claims.

9. One comment suggested that total fat should be the basis for both the cancer and the heart disease health claims because these two diseases generally are considered together under a single dietary guidance goal for moderation in intakes of total fat and saturated fat.

The agency agrees that public health dietary guidelines generally focus on the reduction in total fat as a major, single goal when referring to both heart and cancer risks. However, health claims are specific for a nutrient -disease relationship. Heart disease and cancer relate to dietary factors through different mechanisms.

In the instance of CHD, dietary saturated fat and cholesterol are the major dietary risk factors because they increase blood LDL-cholesterol levels, which increase the risk of heart disease. As noted in the proposed rule (56 FR 60727 at 60739) and discussed above, total fat consumption affects risk of heart disease indirectly, through its effects on obesity and on facilitating dietary reductions in saturated fat and cholesterol. In contrast to the association between dietary fat and heart disease, the observed association between dietary fat and cancer has not been attributed to a specific type of lipid but has generally been linked to total fat intakes (see the final rule on dietary lipids and cancer published elsewhere in this issue of the **Federal Register**.

Health claims must reflect current scientific understanding and agreement as to the basis of a diet-disease relationship. Thus, total fat is not listed as a causal dietary fat in the health claim. Instead, it is addressed as an additional criterion that must be met by a food before it may carry a health claim relating dietary saturated fat and cholesterol to risk of heart disease, because of the strong indirect effect of fat on heart disease risk. Of course, food labels may also include the claim "low fat" in addition to a health claim in accordance with the requirements for such claims, as discussed in the final rule on general requirements for nutrient content claims elsewhere in this issue of the **Federal Register.**

C. Other Qualifying Criteria

10. Some comments recommended that consumption of foods that alter other risk factors for CHD be included as qualifying nutrients relative to the fat/heart disease claim. For example, because foods high in salt or excess calories from sugars may be related to hypertension or obesity, respectively, the comments requested that limits be placed on the amount of salt or sugars that a food bearing this health claim may contain.

FDA recognizes that both hypertension and obesity are risk factors for heart disease and (see the final rule on sodium and hypertension, published elsewhere in this issue of the **Federal**

guidelines, salt and sugars should be used in moderation. However, FDA believes that the arguments for making sugars content a qualifying criterion are considerably less compelling than those for total fat.

FDA has not established a Daily Reference Value for sugars because, other than dental caries, no public health concerns related to sugar have been substantiated (see final rule on Reference Daily Intakes and Daily Reference Values published elsewhere in this issue of the **Federal Register**. A cause-and-effect relationship between sugars intake and obesity is also not well established (Refs. 224 and 225). Conversely, the relationship of fat to obesity is based in part on the fact that fat is a more concentrated source of calories than sugars (9 calories per g versus 4 calories per g). Furthermore, new research suggests that on a calorie-by-calorie comparison, fat calories may be more likely to be laid down as adipose (fat) tissue in the body than carbohydrate calories (including sugar) (Ref.20).

Additionally, since saturated fat and cholesterol constitute pert of the total fat content of foods, most dietary guidelines suggest that it is generally easier to reduce the target nutrients if total fat also is reduced (Refs. 20, 29, 33, 35, 36, 136, 150, and 151). High total, fat intakes are also associated with the risk of cancer (see the final rule on dietary lipids and cancer, published elsewhere in this issue of the **Federal Register**. For these reasons, all current dietary guidelines include reduction of total fat as well ass saturated fat and cholesterol when recommending dietary changes to reduce the risk of heart disease. Similar recommendations are not made for sugars (Refs. 20, 35, 136, and 151).

Thus, FDA concludes that the arguments to make sugars content a qualifying or disqualifying criterion are not convincing based on available data. FDA recognizes that all food nutrients, including sugars, have an appropriate role in the diet.

In the case of salt (and sodium), the issue is more difficult. FDA has found that sodium is a risk factor for hypertension (see the final rule on health claims for sodium and hypertension published elsewhere in this issue of the **Federal Register**). Furthermore, hypertension is considered to be a risk factor for cardiovascular disease, particularly for strokes and, to a lesser degree, for heart disease (Refs. 20 and 30 through 36). In choosing qualifying criteria for authorized health claims, FDA has tried to limit the number of qualifying nutrients to those nutrients that are most strongly linked to the nutrient/disease relationship, based on the current science. In the case of total fat, FDA concluded that it is appropriate to include it as a qualifying criterion because saturated fat is a subcomponent of total fat and because dietary guidelines consistently recommend moderate intakes of saturated fat, cholesterol and total fat.

Sodium is e disqualifying nutrient for the dietary saturated fat and cholesterol/heart disease health claim, as for all health claims (i.e., as finalized, any health claim is prohibited on a food if the food contains 480 mg or more of sodium per reference amount customarily consumed, per label serving, or, if the reference amount is 30 g or less or 2 tablespoons or less per 50 g of food). The suggestion to make sodium a qualifying, rather than a disqualifying nutrient, for this claim is less compelling than the argument for total fat. The link of salt to heart disease is not as direct as the link between saturated fat and cholesterol to heart disease. Dietary guidelines generally deal with sodium and fat separately. If sodium were changed from a disqualifying to a qualifying nutrient, that is, if foods were required to be low in sodium to be eligible for a saturated fat/cholesterol, and heart disease claim, the number of foods that could bear such a claim would be greatly reduced. Foods excluded would include many foods in the following food categories that are generally found to be useful in meeting healthful diets: vegetable products, whole wheat breads, cereals, legume products, and some dairy products (Ref. 222). By retaining sodium as a disqualifying nutrient, not only will a much broader range of useful foods be allowed to qualify for a fat/heart disease claim, but foods in these and other food categories that contain large amounts of sodium will be disqualified. Examples of foods that will be excluded because their sodium content exceeds the disqualifying levels are certain vegetable products such as sauerkraut and some juices, many soups, and some sauces.

11. Several comments recommended that the agency drop the qualifying requirement for saturated fat in proposed § 101.73(a)(3)(iii), in which FBA proposed that the saturated fat content of the food must be less than 1 g per 100 g of food. One comment suggested that the agency instead require that the food be low in saturated fat or have "not more than 7 percent of calories from saturated fat."

The agency was persuaded by the comments that the additional density requirement (per 100 g) for saturated fat is not necessary. The agency was originally concerned that if it used only the definition for "low saturated fat" in the nutrient content claim proposal; the claim could appear on certain fats and oils. However, the agency has recognized that the requirement that a food meet the "low fat" criteria will prohibit foods that are 100 percent fat, such as oils, from bearing that health claim. The agency therefore has dropped the additional qualifying requirement for saturated fat that was in proposed § 101.73(a)(3)(iii). The agency has determined that the food or food product must meet the following qualifying criteria: "low in saturated fat, low in cholesterol, and low in total fat," as described in the rule on nutrient content claims published elsewhere in this issue of the Federal Register and stated in new §101.75(c)(2)(ii).

IV. Safety Issues

In the proposed rule (56 FR 60727 at 60735), FDA noted that reductions in dietary intakes of saturated fat and cholesterol could result In higher intakes of other dietary components (e.g., monounsaturated and polyunsaturated fats, simple and complex carbohydrates, and commercially generated fats), because calories lost from decreased intakes of saturated fats would likely be "made up" by other energy-yielding nutrients. The availability of saturated fat and cholesterol/heart disease health claims will likely motivate manufacturers to alter the amount and type of fats added to foods, resulting in changes in composition of the U.S. food supply. As FDA discusses more thoroughly in the preamble of the final rule on general requirements for health claims, which appears elsewhere in this issue of the Federal Register, changes in consumption patterns may effect whether a food ingredient is safe and lawful under the act. Manufacturers should therefore assure themselves that such consumption changes will not affect the lawful status of the foods containing these ingredients. The agency, in its proposed rule (56 FR 60727 at 60735 to 60737), identified several areas of possible concern regarding changing American dietary patterns.

A. Trans-fatty Acids

One area of potential concern identified in the proposed rule is the potential for increased consumption of trans-fatty acids because of substitution of these fats for SFA's in foods. Trans-fatty acids (generally isomers of *cis*-monounsaturated fatty acids) are primarily constituents of commercially

hydrogenated or hardened natural vegetable oils used in formulating margarine, shortenings, and salad and cooking oils.

12. A number of comments were received, some agreeing and some disagreeing, on the agency 's public health concern that trans-fatty acids may have cholesterol-raising characteristics, and, therefore, may increase the risk of heart disease. These concerns, were raised in response, to the published results of the Mensink and Katan study (Ref. 95). This study assessed the effects of a diet enriched in (trans-fatty acid on blood lipids in 34 healthy women and 25 healthy men. The study results suggested that compared to an isocaloric diet enriched in oleic add (a monounsaturated fat), the *trans*-fatty acid diet significantly increased LDL-cholesterol and significantly decreased high-density lipoprotein cholesterol (HDL-cholesterol) levels (two risk factors for heart disease (Refs. 1, 31, 33, 35, 48, 49, 74, 84, 112, 113, and 187)). (An evaluation of study-design, results, and public health implications is found in the proposed rule (56 FR 60727 at 60736)).

In addition, the potential adverse health effects of *trans*-monounsaturated fatty acids were evaluated in the final version of the 1992 LSRO report on Lipids and Cardiovascular Disease (Ref. 196). This report states that:

> * * * until recently there was the general belief that trans-monounsaturates are "neutral" with respect to serum cholesterol levels. However, the recent findings of Mensink and Katan (1990) strongly suggest that these fatty acids have an adverse effect on serum lipoprotein levels, especially raising LDL-cholesterol levels. Still it hardly seems prudent to alter general dietary recommendations on the basis of a single study, albeit an excellent piece of investigation. Further carefully controlled studies thus appear to be in order before definitive recommendations can be made about trans-fatty acids for the American diet

Other comments stated that "*trans*-fatty acids in foods may increase the risk of CHD equal to or greater than saturated fatty acids." Another comment suggested that "*trans*-fatty acids may increase the risk of coronary heart disease by a mechanism other than by increasing blood cholesterol.'' Another comment referred to *trans*-fatty acids as "deadly trans-fat pollution." Another comment-suggested that the agency require a "warning" label for foods containing significant amounts of *trans*-fatty acids. Several comments suggested that trans-fatty acids should be included in the declaration of total SFA's content because they may have "cholesterol-raising" effects.

One comment on *trans*-fatty acids provided data that suggested that the *trans*-fatty acid content of some foods such as French fries was much higher than reported in commonly used food composition tables (i.e., that a medium serving of French fries from a fast food restaurant contained 7 g of trans-fatty acids, the upper daily limit of consumption, suggested in several authoritative reports). Another comment criticized these data suggesting that proper sampling of the class of analyzed food had not been done.

One comment suggested that cis- and *trans*-monounsaturated fatty acids have similar metabolic actions. No data were provided in support of this comment, although it pointed out that the 1985 FASEB report on *trans*-fatty acid (Ref. 74) concluded that *trans*- fatty acids did not increase the risk of heart disease. One comment was concerned with the negative tone of the discussion on trans-fatty acids and suggested that the cited 1991 study by Mensink and Katan (Ref. 95) on adverse effects of *trans*-fatty acids was limited by its short duration (3 weeks), study population (healthy students), and processing techniques used to generate the hydrogenated *trans*-fatty acid isomers used in the test diets (varying catalyst and time) (Ref. 200). The comment expressed concern, that the *trans*-fatty acids used in the test diets differed from those most commonly found in the U.S. food supply (i.e., different positional isomers), and that the *trans*-fatty acids may have been consumed in larger quantities in the test diets than they are generally consumed in the United States. The comment further suggested that a combination of these factors may have created a situation in which the study results suggesting that the consumption of diets enriched in *trans*-fatty acids increase blood LDL-cholesterol levels and decreased blood high density lipoprotein HDL-cholesterol, a blood cholesterol component for which low levels are associated with increased CHD risk (Refs. 1,47 through 49, 74, 75, 112, 113, and 187) were not necessarily applicable to the U.S. population. One comment referred to the report of Nestel (Ref. 177), which compared the effect of edible vegetable oil blends containing hydrogenated fatty acids on serum lipids. (The diets and study design are described in Table 1 of this document.) The results of this study showed that low saturated tat test diets containing *trans*-fatty acids from different oil sources lowered blood total cholesterol and LDL-cholesterol levels significantly as compared to control diets high in saturated fat.

Among the other comments on the study by Mensink and Katan (Ref. 95, 56 FR 60737 at 60736), was a referral to a published article written by Mensink and Katan (Ref. 201) which addressed criticisms of their 1990 study by noting that another study of longer duration (16-weeks), conducted in the same laboratory, found a similar effect on blood cholesterol levels, even after only 2 weeks on the diets (Ref. 201). One comment suggested a need for further research in the area of *trans*-fatty acids and blood cholesterol Ie1 vets before policy decisions are made.

The agency agrees in general with the conclusions of the 1992 LSRO report that, while the available evidence to date is suggestive that *trans*-monounsaturated fatty acids may have LDL-cholesterol-raising characteristics, there is insufficient evidence upon which to make policy decisions at this time. FDA also notes that the requirement that foods be "low"' in total fat before making a fat/heart disease health claim, limits a manufacturer's ability to increase, *trans*-fatty acid levels in foods, since any substitution of *trans*-fatty acids for SFA's must be done within the 3 g per reference serving size or per 50 g, limit for total fat. This approach, is unlikely to result in significantly increased levels of *trans*-fatty acids in foods qualifying for a health claim. The agency may reconsider the relationship of *trans*-fatty acid to heart disease claims at a later date if new data become available to confirm and strengthen the initial findings of an adverse effect of *trans*-fatty acids on blood LDL- and HDL-cholesterol levels. Results from well-designed scientific studies on the effect of *trans*-fatty acids at, or slightly above, current U.S, consumption levels on blood lipids levels and on other risk factors for cardiovascular disease will aid the agency in reaching future decisions.

B. PUFA's

In the proposed rule, FDA expressed concerns about possible safety problems associated with consumption of diets enriched in polyunsaturated fats because of the substitution of these fats for SFA's (56 FR 60737 at 60736). Among concerns that FDA raised were potential adverse effects on cell membrane fluidity (a possible risk factor for cardiovascular disease (Ref. 20); decreasing levels of blood. HDL-cholesterol; increase in formation of lipid hydroperoxides (oxidized LDL-cholesterol has a high atherogenic potential, Ref. 132); increasing blood

triglyceride levels (a possible risk factor for heart disease (Ref. 187); and increasing the risk of some types of cancer (see the proposed rule on dietary lipids and cancer at 56 FR 60764, November 27, 1991).

13. Many comments raised issues concerning the question of the safety of PUFA's in foods and supplements. Comments suggested that safety issues related to PUFA's included increased risk of cancer, coronary thrombosis, and osteoporosis in humans. A few comments also stated that PUFA's may adversely affect immune function. Conversely, others disagreed with the statement in the proposal that PUFA's may increase predisposition to or frequency of certain types of cancer because none of the dietary consensus documents of the Federal Government identified PUFA's as a risk factor for cancer in humans. One comment disagreed that diets enriched in PUFA's may decrease HDL-cholesterol levels but did agree with the description of results from the study by Wardlaw in Table 2 of the proposed rule (56 FR 60727 at 60764 (Ref. 144)) that, "High concentrations of PUFA's may have pharmacological effects on lowering HDL-cholesterol, however, diets containing 35 percent of calories from fat and a polyunsaturated saturated fatty acid (P:S) ratio of less than 1.5 are not likely to lower HDL-cholesterol significantly." One comment suggested that diets high in PUFA's (greater than 10 percent of calories) cannot be achieved by the American public, so the potential safety concerns were overly emphasized.

The LSRO report on "Lipids and Cardiovascular Disease," submitted as a comment to the record, separated the evaluation of PUFA's into two categories: omega-6 polyunsaturates and omega-3 polyunsaturates (Ref. 196). Relative to linoleic acid (one of the major types of omega-6 fatty acids in the U.S. diet and an essential fatty acid), the report noted that while:

> * * * higher intakes may slightly reduce LDL-cholesterol * * * a higher consumption may increase risk for some cancers, promote LDL oxidation with the arterial wall, and possibly raise the risk for coronary thrombosis * * *. A reasonable recommendation may be to avoid both excessively low intakes of linoleic acid (below 4 percent of calories) and higher intakes (above 7 percent of calories).

Relative to the second type of PUFA's, the omega-3 fatty acids, the LSRO report noted that:

> Recommendations for increasing omega-3 fatty acids for the purpose of preventing common chronic diseases must be made with caution and only after more conclusive data are available * * *. Since these fatty acids are biologically active, they deserve intense investigation, but not premature recommendations for their consumption by the general public.

FDA agrees with the concern that high levels of intake of PUFA's have the potential for adverse effects in some persons. However, when consumed in amounts similar to current intakes, little or no risk is anticipated (Refs. 20, 29, 31, 33, 35, 74, 78, 136, and 196). Indeed, adequate intakes of essential fatty acids are needed to prevent nutrient deficiencies. By requiring that a food be low in total fat as a qualifying criterion, FDA has made it unlikely that excessively high intakes of PUFA's will be encouraged through the use of a health claim, because there is little room for manipulation of different fats within this range for total fat. Given current levels of intake of essential fatty acids by the U.S. population, deficiencies are not anticipated (56 FR 60727 at 60738; also, see document on dietary lipids and cancer published elsewhere in this issue of the **Federal Register**.

C. Other Safety Issues

14. One comment expressed concern about foods that qualify for a health claim for lipids and cardiovascular disease but that contain a nutrient that may increase the risk of cardiovascular disease or another disease or disorder. As an example, the comment suggested skim milk, which contains no or low fat and cholesterol but does contain casein. The comment suggested that casein has been reported to have atherosclerotic properties in some animals, but no data were provided to support this comment.

The basic concept of this comment, that the use of foods bearing health claims should not unduly increase the risk of disease because of the level of nutrients other than the nutrient that is the subject of the claim, is mandated by section 403(r)(3)(A)(ii) of the act. The preamble of the final rule concerning the general requirements for health claims, which appears elsewhere in this issue of the **Federal Register**, contains an extensive discussion of the agency's implementation of that section of the act through disqualifying nutrient levels.

FDA, however, disagrees with the specifics of this comment, i.e., that casein should be considered a negative component that would disqualify a food from bearing a fat/heart disease claim. FDA is aware of early research suggesting that casein has possible adverse effects on risk of heart disease (Ref. 20). However, these observations have never gained wide acceptance by the scientific community, and casein (a rich source of protein) is not considered to significantly contribute to the risk of heart disease.

V. Miscellaneous Issues

The proposal contained a number of additional provisions addressing both mandatory and optional aspects of claims about lipids and cardiovascular disease in proposed § 101.73(a)(4) and (a)(5). Proposed § 101.73(a)(4)(i) provided that a claim must state that a diet low in saturated fat and cholesterol will reduce high blood cholesterol and, thus, the risk of coronary heart disease. Proposed § 101.73(a)(4)(ii) provided that health claims must include the caveat that "some but not all individuals" would benefit from these dietary changes. Also the terminology for heart disease, blood lipid levels, and dietary fats were described in proposed § 101.73(a)(4)(iii)(A), (a)(4)(iii)(B), and (a)(4)(iii)(C). Furthermore, information on the multifactorial nature of the disease and other risk factors was included as a specific requirement in proposed § 101.73(a)(4)(iv), and optional information on the need for medical guidance and on the prevalence of heart disease in the U.S. population was provided in proposed § 101.73(a)(5)(i) and (a)(5)(ii), respectively. Many of these provisions are addressed in the following comments.

15. Some comments questioned the applicability of a claim relating diets low in saturated fat and cholesterol to reduced risk of heart disease in the general U.S. population. These comments asserted that only about 25 percent of the population may be responsive to reduction in dietary cholesterol and saturated fat. Thus, the comments argued, it would be misleading to imply that all persons would benefit. Conversely, me LSRO report concluded that "all people in the United States * * * will potentially benefit * * * from reductions in dietary saturated fat" (Ref. 196). Relative to dietary cholesterol, the LSRO report noted that " * * * avoidance of high intakes of dietary cholesterol for the whole population is prudent." Another comment suggested that the agency prescribe the term "most" individuals, persons, or people in referring to those people who may benefit from these dietary changes rather than "most but not all people."

As discussed in the proposed rule (56 FR 60727 at 60740), FDA recognizes that the beneficial effects from reduction of intakes of saturated fat and cholesterol are highly variable among individuals, particularly in terms of magnitude of effect. For this reason, FDA proposed to require that health claims make clear that the effects described in the claim

are likely to be realized by "some but not all persons" (proposed § 101.73(a)(4)(ii)). At the same time, FDA does not wish to imply that a health claim on dietary lipids and heart disease in accordance with this rule is not useful information for the general population. Current dietary guidelines and the LSRO report cited above conclude that, even if responses among individuals are variable in magnitude, the majority of the population, including persons with normal blood cholesterol levels, will benefit from these dietary goals (Refs. 20, 29 through 36, 74, 136, and 151). Given the strong scientific agreement that the majority of persons in the U.S. will benefit from a reduction in intake of saturated fat and cholesterol, FDA has concluded that the proposed term "some persons but not all" is too conservative. FDA has thus not included any requirement for indicating that the nutrient/disease relationship is limited to "some persons but not all" in the final rule. Therefore, new § 101.75(c)(2)(i)(A) reads: "The claim states that diets low in saturated fat and cholesterol 'may' or 'might' reduce the risk of heart disease;".

16. Several comments recommended that the agency require that health claims include a statement on seeking medical advice for persons with multiple risk factors for heart disease. These comments suggested that the majority of the population at risk of cardiovascular disease may require medical advice and may need a combination of medication and diet and lifestyle changes. For these persons, adopting a diet low in saturated fat and cholesterol may not substitute for aggressive medical intervention.

FDA agrees that persons with blood LDL-cholesterol levels in the moderate to high risk ranges and with multiple risk factors for heart disease should seek medical advice. However, as noted above, dietary goals for intakes of saturated fat and cholesterol have been recommended for the general population as well as for persons with elevated blood cholesterol levels because of findings of benefit across the entire range of blood cholesterol levels (Refs. 31 and 33). FDA is concerned, therefore, that to require a statement that persons seek medical advice and guidance as part of the health claim might give the erroneous impression to consumers that there is no benefit for them in making the recommended dietary changes unless they have been identified as high risk patients. For this reason, FDA is not persuaded to change the status of information on medical advice from an optional to a mandatory requirement. Thus, the agency is retaining this provision as an optional statement in new § 10 75(d)(7), which states:

> The claim may state that individuals with elevated blood total- or LDL-cholesterol should consult their physicians for medical advice and treatment. If the claim defines high or normal blood total- or LDL-cholesterol levels, then the claim shall state that individuals with high blood cholesterol should consult their physicians for medical advice and treatment.

17. The agency proposed in § 101.73(a)(4)(iv) that the health claim may state that CHD is a multifactorial disease and listed major risk factors for the disease that may be used in the claim. This provision was worded so as to suggest that providing the above information was optional. However, this provision was included among the specific requirements in § 101.73(a)(4).

The agency received comments that both supported and opposed FDA requiring that any health claim describe CHD as a multifactorial disease. Several comments suggested that the multifactorial nature of the disease should be referred to indirectly, while other comments suggested that these multiple factors should be required to be identified in the health claim. Some comments identified a number of modifiable dietary risk factors for cardiovascular disease not included among those listed the proposed health claims such as: sodium (56 FR 60825), fiber (56 FR 60582), and antioxidant vitamins (56 FR 60624). Other comments recommended that the agency require that the most important risk factors for CHD, elevated LDL-cholesterol, high blood pressure, and cigarette smoking, be listed.

FDA recognizes that its proposal was inadvertantly ambiguous about whether the fact that CHD is a multifactorial disease would be a required element of the health claim on dietary lipids and this disease. As pointed out in the proposal (56 FR 60726 at 60740), given the multiple dietary, genetic, and lifestyle risk factors for this disease, consumers would be misled if they were to think that dietary factors are the only risk factors. Given this fact, FDA has concluded that the multifactorial nature of the disease should be a required element (§ 101.75(c)(2)(i)(E)).

The issue that is raised as a result is how the significant risk factors should be presented. FDA is concerned that encouraging an unrestricted listing of risk factors for heart disease could result in the listing on food labels of risk factors with relatively little importance or minimal scientific support or could be used to bypass other label requirements. For example, some comments listed several nutrient risk factors for heart disease, including sodium intake. While FDA is authorizing the use of sodium/hypertension health claims, the agency has not been presented with evidence that sodium intake is a risk factor for heart disease. A claim characterizing the relationship between sodium and heart disease is a health claim and would misbrand a food under section 403(r)(1)(B) of the act unless it is specifically authorized by the agency. Thus, the comments suggested that some would use a list of factors as a backdoor means of making unauthorized health claims. As a result, FDA concludes that only the significant risk factors should appear as part of a health claim. For example, those factors that identify the populations that are at risk, where the general population is not at risk, are appropriate for inclusion in the claim. Listing risk factors that are not significant would be false or misleading and could, as explained above, misbrand the food under section 403(r)(l)(B)of the act.

While FDA has decided that the fact that coronary heart disease is multifactorial should be a mandatory element of nutrition labeling, it has also decided that the specific risk factors need not be. As discussed below in conjunction with model health claims. FDA has received numerous comments that the shorter health claims are, the more likely it is that they will be used and understood. Therefore, given the information that it is requiring, FDA has decided, that on balance, it is not necessary to include the significant risk factors as mandatory elements of a claim.

The listing of risk factors provided in proposed § 101.73(a)(4)(iv) represented scientific consensus as to the most significant factors for heart disease. In this final rule, FDA has redesignated the list of risk factors in proposed § 101.73(a)(4)(iv) as new § 101.75(d)(1). This section provides a list of the factors that, based on general scientific agreements are the major factors for heart disease. The agency has also provided that any list of risk factors included as part of a health claim may include one or more of these factors but must be limited to the factors on this list. Thus, new § 101.73(d)(1) states that:

> The claim may identify one or more of the following risk factors in addition to saturated fat and cholesterol about which there is general scientific agreement that they are major risk factors for this disease: a family history of coronary heart disease, elevated blood LDL-cholesterol, excess body weight, high blood pressure, cigarette smoking, and long-term physical inactivity.

18. Other comments pointed out that, while excessive intake of some nutrients such as fat may be harmful, there are also minimum intake levels which are essential. Some of the comments suggested that the agency identify minimum thresholds levels for SFA's, MUFA's, PUFA's, total fat and other dietary nutrients below which intakes should not drop. The comments expressed concern that intakes below these levels would increase risk of nutrient deficiencies.

FDA recognizes that there are intake levels for nutrients below which there may be a risk of nutrient deficiencies that could present a risk of adverse effects. FDA disagrees, however, that these levels should be included in the health claim on dietary saturated fat/cholesterol and heart disease. In the proposed rule for a health claim on lipids and cardiovascular disease and as stated in the proposed rule on dietary lipids and cancer, FDA noted that:

> The requirement of linoleic acid to avoid essential fatty acid deficiency is 1 to 2 percent of total calorie intake. Currently, the average linoleic acid consumption in the U.S. ranges between 5 and 10 percent of total calorie intake, and deficiencies of essential fatty acids are rare in the U.S. Thus, a reduction of total fat consumption from the current 36 to 37 percent of total calorie intake to about 30 percent is not likely to cause essential fatty acid deficiencies in the general population.

(56 FR 60764 at 60712)

Furthermore, as previously noted in the response to comment 14 of this document, the reduction of saturated fat intakes to meet dietary goals for reduction in risk of heart disease is likely to result in increased intakes of PUFA—the source of the essential fatty acid, linoleic acid. Thus, FDA concludes, as was also concluded in several authoritative reports (Refs. 20, 29, 35, 136, and 150), that there is little likelihood of nutritional deficiencies relative from changes in U.S. dietary patterns in response to health claims relative to saturated fat/cholesterol and heart disease.

19.One comment suggested that health claims not be allowed on foods that have been modified to meet the "low fat," "low saturated fat" or "low cholesterol" requirements unless the foods are nutritionally equivalent to the unmodified versions of those foods. FDA rejects this comment. The issue of the effects of a failure to maintain nutritional equivalency are fully addressed by §101.3(e) of FDA's regulations, and in the final rule on standardized foods named by use of a nutrient content claim and a traditional standardized term, published elsewhere in this issue of the **Federal Register**. As long as a food meets the requirements of those regulations, § 101.14, and § 101.75, it may bear a health claim on the relationship of saturated fat and cholesterol and coronary heart disease.

20. One comment asked the agency to reconsider its position that health claims are inappropriate for foods intended to be consumed by infants and toddlers of less than 2 years of age; second, to reconsider the amount of total fat, saturated fat and cholesterol that meet requirements for health for infants and toddlers; third, to reconsider the age when infants and toddlers should start to consume "low fat" diets. The comment recommended that low saturated fat, low cholesterol, and low fat diets should be extended to even earlier ages, and that the percent of calories from fat for infants and toddlers should be less than 30 percent to reduce obesity, a risk factor for heart disease. The comment did not submit scientific data to support the proposition that a reduction in heart disease would occur if infants and toddlers consumed low fat diets (i.e., less than 25 percent of calories) earlier than 2 years of age.

FDA disagrees with the comment. In the 1990 amendments, Congress indicated that, if FDA's decision on a health claim petition deviated from recommendations of the Federal Government, those differences should be justified (section 403(r)(4)(C) of the act). The agency based its conclusions on the report from the National Cholesterol Education Program (NCEP) on population strategies for healthy children and adolescents (56 FR 60727 at 60731 (Ref. 34)). This report stated that general dietary recommendations for diets low in saturated fat, cholesterol, and total fat should be extended to cover toddlers and children 2 years and older. FDA has seen no compelling evidence to counter the conclusions of the NCEP report.

21. Several comments Supported the agency's proposed limitation in proposed § 101.73(a)(4)(iii) on interchangeable terms for the disease, for lipids levels, and for the nutrients involved. Another comment suggested that the term "low density lipoprotein cholesterol" or the term "LDL-cholesterol" be used in place of the term "total blood cholesterol."

FDA agrees that the term "LDL-cholesterol" is more precise than the term "blood total cholesterol," but disagrees that it should be used in place of the term "total blood cholesterol" in § 101.75(d)(2) of the final rule. FDA, in proposing the term "total blood cholesterol" was using language commonly used in dietary guidance materials at the time of the proposal. Since the publication of the proposal, the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) held a consensus conference on Triglycerides, High Density Lipoprotein, and Coronary Heart Disease in February 1992 (Ref. 187). As a result of that conference, a consensus panel draft report was published reconfirming that high levels of blood LDL-cholesterol are associated with high risk of CHD. The consensus conference panel draft report also concluded that low levels of another blood cholesterol component, HDL-cholesterol, in conjunction with high levels of LDL-cholesterol, were associated with a higher risk of heart disease. These two different cholesterol transport components of blood cholesterol when considered in combination are better predictors of risk than when considered independently.

The agency believes that the term "blood total cholesterol" should be retained to minimize consumer confusion, since that term is used in dietary guidance materials and many consumers know their blood total cholesterol levels. However, the agency believes that consumers will eventually learn that high LDL-cholesterol levels are strongly associated with risk of heart disease and are reduced by diets low in saturated fat and cholesterol in most people. The agency has therefore specified in new § 101.75(d)(2) that the term "LDL-cholesterol" may optionally be used in addition to the term "blood cholesterol," and states: "The claim may indicate that the relationship of saturated fat and cholesterol to heart disease is through the intermediate link of "blood cholesterol" or, "blood total- and LDL-cholesterol."

In other respects, the agency is carrying forward the terminology from the proposal in new § 101.75(c)(2)(i)(B), the agency is limiting the terms used to specify the disease to heart disease or coronary heart disease. This provision is consistent with proposed §101.73(a)(4)(iii)(A). Furthermore, in new § 101.75(c)(2)(i), the agency retains the limitations on specifying the nutrient in proposed § 101.73(a)(4)(iii)(C). However, § 101.75(c)(2)(i)(C) states that^lB specifying the nutrient, the claim uses the terms 'saturated fat' and 'cholesterol,' and lists both;".

22. One comment requested that health claims relating to lipids and cardiovascular disease be allowed for fruits and vegetables, which are naturally low in saturated fat, total fat, and cholesterol.

FDA agrees that fruits and vegetables should be allowed to bear appropriate health claims. The agency notes that because most fruits and vegetables are naturally low in saturated fat and do not contain cholesterol, they will meet the qualifying criterion of new § 101.62 for "low saturated fat," "low cholesterol," and "low total fat," and thus will qualify under § 101.75(c) to bear this claim.

FDA advises that it has made a couple of additional minor changes in § 101.75. The agency has added § 101.75(a)(1), which, consistent with other regulations that the agency is adopting that authorize health claims, defines some of the terms in the regulation. These definitions are consistent with generally accepted science and with the discussion in the proposal. In addition in § 101.75(d)(5), FDA has added the National Institutes of Health and "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 29) in recognition that both are sources of information on the number of Americans with heart disease.

VI. Model Health Claims

23. Several comments suggested that the model health claims should be reduced in length. Some suggested that health claims should follow examples established by the Surgeon General's office, keeping the health claim in a precise, easily understandable text. One manufacturer submitted model health claims and examples of labeling. One comment submitted an example of a possible health claim: "Eating a healthful diet low in fat, saturated fat and cholesterol can help reduce the risk of heart disease." Another comment suggested that the health claim should state; "This ———— can be part of a total diet low in saturated fat and cholesterol, which can reduce risk of heart disease. Use in place of more saturated fats as part of a diet low in total fat. Contains ———— grams of saturated fat, ———— grams of total fat per serving." Another comment recommended an additional statement to be added to the health claim: "In vitro and animal data are often useful for formulating research hypotheses, but can be inappropriate and unreliable for making public policy."

FDA agrees with the comments that, to the extent possible, the model health claims should be shortened and made more understandable. They are more likely to be used by manufacturers if they take up as small an amount of label space as possible. Consumers will be more likely to read messages if they are stated simply and succinctly. However, section 403(r)(3)(B)(iii) of the act requires that health claim regulations ensure that claims accurately represent the nutrient/disease relationship and its significance and enable consumers to understand the information and its significance in the context of the total daily diet. Thus, there are constraints on FDA's authority to penult claims to be abbreviated.

The issue of shorter health claims has been discussed in detail in the preamble to the final rule on general requirements for health claims published elsewhere in this issue of the **Federal Register**. As noted in comment 15 of this document,. FDA has dropped the phrase "in some but not all." Additionally, FDA is making reference to the blood cholesterol linkage between dietary saturated fat and cholesterol and risk of heart disease optional. FDA reasons that this amount of detail is not necessary to motivate consumers to implement recommended dietary changes and contributes to wordiness. Thus, the minimum requirements can now be met with a statement as simple as "While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease." Additional provisions that were included in the proposed rule have been deleted or made optional to simplify health claims. Other model health claims are provided in new § 101.75(e). As discussed earlier in this preamble, FDA does, however, believe it is important for each model health claim to acknowledge that many factors affect heart disease.

Other changes incorporated into the final regulation include reorganization of paragraphs and clarification of requirements. The final regulation requires claims to use the word "may" or "might" rather than "can" or other words when describing the possible effect of a diet low in fat and cholesterol on risk of heart disease (§101.75(c)(2)(i)(A)). Although FDA recognizes that it cannot require preclearance of claims, it considers this and other restrictions on word choices to be necessary so that claims will accurately reflect the state of the science. All changes in the final regulation are a logical outgrowth of the proposal.

24. A few comments suggested that the agency amend the language of the health claim to include "very-low fat, low-cholesterol diets begin to reverse CHD in some patients." Accompanying the comments were six scientific publications describing six clinical trials. The comments thus suggested tighter criteria for the qualifying levels of fat and cholesterol, e.g., "very low," and a replacement of "may reduce the risk of" with a stronger statement about a "reversal" of CHD. In addition, the suggested claim would target one segment of the general population which is at increased risk for heart disease. The comments submitted a number of publications to justify use of the term "reversal" of heart disease.

FDA does not agree that the submitted publications justify the statement that heart disease may be reversed by very low fat, low saturated fat, and low cholesterol diets. Three of the randomized, controlled trials were previously reviewed (in Table 2 of the proposal) by the agency (56 FR 60727 at 60754 through 60755 and 60763) (Refs. 12, 14, and 106). The fourth was conducted in 1984 (Ref. 197) and therefore evaluated by Government and other public health authoritative reports, and the two remaining studies did not provide adequate information to be able to attribute beneficial results to specific dietary components (Refs. 198 and 199). Thus, while FDA finds these results very interesting and considers the studies to suggest a decrease in progression of heart disease from the combination of medical interventions used in these studies, FDA has concluded that these results are not applicable to health claims for several reasons. First, the treatment modality used to obtain results was primarily drugs that lower both blood lipids and blood pressure, in combination with dietary changes. Secondly, the treatment changes were quite severe, and their implementation in the general population is unlikely to be a reasonable goal. Finally, subjects were persons with serious preexisting CHD and under close medical supervision.

25. 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. The comment asked that the health claim be required to specifically identify and target this group of individuals as high-risk populations.

FDA disagrees that specific dietary advice and goals for persons with diseases such as noninsulin-dependent diabetes mellitus and hyperlipidemia should be required to be included as part of health claim messages. These are serious health conditions and require medical supervision. Health claims are intended for the general population. Foods bearing claims for conditions requiring medical supervision are more appropriately regulated as foods for special dietary use, as medical foods, or as drugs, depending upon the specifics of the food and the claims made for it.

VII. Consumer Summary

FDA also proposed to make available consumer summaries to provide additional information on the health claim. Comments from consumers, health care professionals, public health associations, and the food industry supported the use and availability of consumer summaries. FDA did not receive any comments that did riot support the use of consumer summaries for this health claim regulation. Comments were received, however, for other health claim regulations suggesting that there was no need for consumer summaries.

As discussed in the final rule on general requirements for health claims published elsewhere in this issue of the **Federal Register**, consumer summaries are not required, although their use remains an option. For this reason, the proposed consumer summary has not been included in this final rule.

VIII. Summary of Updated Science Review

To ensure that significant new evidence had not become available subsequent to the proposal. FDA updated its review of the scientific evidence with human studies that were directly relevant to the proposed rule or that became available after publication of its proposal (Table).

A. Relationship of Dietary Saturated Fat and Cholesterol to Blood Cholesterol and, Therefore, to Risk of Heart Disease.

1. Saturated Fat

In the proposed rule (56 FR 60727 at 60728), FDA accepted the conclusions of consensus documents that serum cholesterol levels are a valid intermediate predictor of risk of heart disease (Refs. 20, 29 through 36, 74, 136, 150, and 151). FDA limited its evaluation of the nutrient/disease relationship to diets low in saturated fat and cholesterol and reduced risk of CHD. FDA additionally proposed that health claims should be prohibited on foods that are not low in fat because of strong indirect links between high fat diets and risk of heart disease.

A recent study supports the applicability of dietary modifications to children. A longitudinal study in 108 healthy Hispanic preschool children (Ref. 183) compared children in the highest tertile (a tertile is a comparison based on thirds, i.e., highest, middle and lowest tertile) of total fat and saturated fat consumption (36.2 percent and 14.6 percent of calories as fat and saturated fat, respectively) to children in the lowest tertile (30 percent and 11 percent of calories as fat and saturated fat). Higher total fat and saturated fat intakes were associated with higher blood total and LDL- cholesterol levels (Table).

Several new clinical trials provide additional support that reductions in intakes of dietary saturated fat and cholesterol reduce serum total and LDL-cholesterol levels, even though serum triglyceride and HDL-cholesterol levels do not change significantly.

Deneke et al. (Ref. 162) compared the effects on blood cholesterol levels in 10 men, mean age 66, (Table) of isocaloric, liquid diets differing in type and amount of SFA. In the self controlled, cross-over study, the saturated fat was derived from either butter (25 percent SFA), beef (18 percent SFA), cocoa butter (23 percent SFA) or olive oil (8 percent SFA). These fat diets also differed in the amount of stearic acid: 4, 7, 6, 13 and 1.2 percent, respectively. Diets enriched in saturated fat from butter, beef, or cocoa butter, significantly increased total cholesterol and LDL-cholesterol compared to diets containing less saturated fat. The higher concentration of stearic acid in both beef and cocoa butter diets did not negate the effect of saturated fat on blood cholesterol levels. Under the conditions of the study design, stearic acid was neutral in its ability to change blood cholesterol levels. This study should be repeated using more subjects, including healthy subjects, and with solid foods to provide nutritional data that is more applicable to the general public.

In another dietary intervention study, the effects of a low fat, low saturated fat, no cholesterol diet on serum cholesterol was reported (Ref. 184). Five familial hypercholesterolemic (FH) patients and four healthy control individuals consumed a diet that was very low fat (8.2 percent of calories), and high carbohydrate (90.5 percent of calories) for 1 month, following 1 month on a basal diet, and after 3 months on a wash-out diet (see Table). Both normal controls and FH patients responded similarly, with a significant decrease in total and LDL-cholesterol. HDL-cholesterol decreased nonsignificantly, but serum triglycerides increased significantly. One difference in response by FH patients and controls to the diets was observed in cholesterol synthesis. Cholesterol synthesis fell 24 percent (8.4 to 6.4 mg/kg/day) in controls and 58 percent (11.4 to 4.8 mg/kg/day) in FH patients.

Another dietary intervention study compared the effects of diets supplemented with saturated fat or linoleic acid on blood cholesterol levels (Ref. 180). This study of free-living subjects was conducted in 12 mildly hypercholesterolemic individuals (5 men and 7 women) ages 27 to 74 years, in a randomized, cross-over design that provided 2 weeks on the basal diet and 3 weeks on each of the test diets. Total fat composition of the diets is shown in the Table. The test diets contained an additional 17.3 percent SFA or 14.8 percent of PUFA (in the form of linoleic acid). The saturated fat-enriched diet significantly increased total cholesterol and LDL-cholesterol compared to the baseline diet The linoleic-supplemented diet, which has a similar concentration of saturated fat as the basal diet, produced significantly lowered total cholesterol, 19 mg/decaliter (dL) (0.5 millimoles/Liter (mmol/L)) less compared to the basal diet and 39 mg/dL (1.0 mmol/L) less compared to the saturated fat-enriched diet. This study should be repeated using more subjects including healthy subjects and with solid foods to provide nutritional data that are more applicable to the general public. The study does suggest the possibility of more flexibility in dietary options available for the general public.

The effect of a "Western" diet rich in saturated fat and cholesterol (total fat, saturated fat and cholesterol: 43 percent, 21 percent, of calories, 1,020 mg/day, respectively) on blood cholesterol levels was measured in free-living subjects who normally consume a low fat, low saturated fat, Tarahumara diet (less than 20 percent of calories from total fat, 7 percent from saturated fat and less than 50 mg/day) (Ref. 176). The study included 12 adults (5 women) and one 12-year-old boy. After consumption of the "Western" diet for 5 weeks, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides increased significantly in all subjects. Total cholesterol increased from 121 mg/dL at baseline to 159 mg/dL, and LDL-cholesterol went from 72 to 100 mg/dL. The "Western" diet as described by the study design contains a higher level of total fat, saturated fat, and cholesterol than consumed by the U.S. general population.

2. Dietary Cholesterol

In another recent study, the effect of dietary cholesterol (in the form of eggs) on serum cholesterol levels was measured in seventy 18 to 19 year old, free-living, healthy males (Ref. 190). A baseline diet containing 3 eggs per week was consumed by all subjects for 3 months (diet composition contained in the Table: total fat was 40 percent of approximately 3,350 calories per day). The subjects were divided into three groups of approximately equal numbers:

one group continued on the baseline diet/group 2 was supplemented with 7 eggs per week, and the third group was supplemented with 14 eggs per week for an additional 5 months. No significant differences were reported in total cholesterol, LDL-cholesterol, or triglycerides between groups.

The authors proposed several suggestions to explain these results. They stated that the relatively high levels of total fat compounded with a low content PUFA compared to SFA content may have canceled the potential serum cholesterol-raising effects of dietary cholesterol. Secondly, they suggested that the subjects may have adapted to the diet by decreasing cholesterol synthesis or by increasing the rate of cholesterol eliminated Item the body.

Meta-analysis was used to examine the effects of dietary cholesterol on serum cholesterol from 76 studies that had reported completely controlled diets (Ref. 221). This meta-analysis, unlike previously reported studies, included baseline together with added dietary cholesterol data, PUFA and SFA content of the diet, and weighted the number of subjects in each trial. The diets used in the trials included formula diets, semipurified diets, and diets based on customary food. The baseline dietary cholesterol was a statistically stronger predictor of change in blood cholesterol than added dietary cholesterol. Thus when baseline dietary cholesterol was high, added dietary cholesterol resulted in diminished increases in total blood cholesterol. Therefore, when one to two eggs are added to a diet that already contain 350 to 400 mg/day of cholesterol, little increase in blood cholesterol would be expected.

B. Estimates of Change in Blood Cholesterol by Following Low Fat, Saturated Fat and Cholesterol Dietary Guidelines

In the following group of studies, the effectiveness of diets reduced in total fat, SFA, and cholesterol to levels suggested by national nutritional guidelines and health organizations were evaluated.

A diet referred to as "US74" (fat content was 38 percent of total calories, SFA 18 percent, MUFA's 34 percent, PUFA 4 percent, and cholesterol 600 mg/day) (Table, Ref. 168) was compared to the diet recommended by U.S. public health authorities (fat 30 percent and SFA, MUFA, and PUFA 10 percent of total calories, respectively, and cholesterol 300 mg/day and referred to as modified diet ("MOD" diet)) on total blood cholesterol levels. The study included 5 free-living women of Chinese origin and 14 of Caucasian origin, in a cross-over, randomized order design with each test diet lasting 3 weeks. Throughout the intervention study, the Chinese women had consistently higher total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels than Caucasians, regardless of diet selected. Caucasian women showed a significant decrease in total cholesterol and LDL-cholesterol only when the US74 diet was compared to the MOD diet. Consumption of the US74 diet increased total cholesterol and very-low density lipoprotein-cholesterol (VLDL-cholesterol) in Chinese women compared to a self selected diet (in which fat was 34 percent of total calories and SFA was about 12 percent, MUFA was 13 percent (based on g of oleic acid/day). PUFA was 8 percent (based on g of linoleic acid/day), and cholesterol was 360 mg/day).

The second study evaluated the effectiveness of the American Heart Association (AHA) Step-1 diet in lowering blood cholesterol in free-living subjects (Ref.154). (The AHA Step-1 diet contains 1.0 percent or less saturated fat; 30 percent or less of total calories from fat: and less than 300 mg/day cholesterol.) Forty-nine men and 38 women completed the 18 week dietitian-instructed study (they were hypercholesterolemic, total cholesterol 243 mg/dL. and LDL-cholesterol 169 mg/dL; and, mean age of 50 years, Table). Modest, but significant, decreases were observed in total-cholesterol and LDL-cholesterol after 6 weeks. No further reductions in total- or LDL-cholesterol were observed at 12 or 18 weeks, and there was a tendency to return to or exceed baseline cholesterol levels. The authors suggested that since most of the participants knew they were hypercholesterolemic before the study, they may have already been following a self-developed, low saturated fat, low fat, low cholesterol diet. This conclusion was derived from analysis of self-administered food frequency questionnaires and 4-day food records, including 1 weekend day collected on baseline diet and AHA Step-1 diets.

The third study compared, the effectiveness of the AHA Step-3 diet with a typical American diet. It pointed out additional considerations in implementing dietary changes to reduce blood cholesterol and CHD risk in women. In the study, 19 free-living premenopausal women consumed a typical American diet for 28 days prior to 5 months of the AHA Step-3 diet (Table, Ref. 161). In brief, self-reported dietary fat, saturated fat, and cholesterol for the American versus AHA Step-3 diet was 37 percent versus 21 percent; 15.7 percent versus 4.7 percent; and 271 versus 96 mg/day, respectively. Total cholesterol, LDL-cholesterol, and HDL-cholesterol decreased in these women consuming the AHA Step-3 diet. However, only after subdividing the women by body mass index were there significant decreases in total cholesterol, LDL-cholesterol, and HDL-cholesterol. Lean women, as determined by body mass index, had significant decreases in blood cholesterol, while moderate or grossly obese women did not. The authors suggest that results from this study with free-living individuals may imply that obese women may be more sensitive to dietary carbohydrates and therefore not as responsive to a diet low in total fat, saturated-fat, and cholesterol and enriched in carbohydrate (43.8 versus 59.4 percent). Secondly, alternative diets that replace SFA by means other than carbohydrate exchange may be more effective in these individuals.

In a fourth study, the effectiveness of intensive dietary instruction on reduction of serum cholesterol level was evaluated as part of the Heart Tune Program (Ref. 169). Hypercholesterolemic patients (30 women and 19 men) attended 4 consecutive classes on heart disease, properties and definitions of fat, healthy food selections, and meal preparations for 2 1/2 hours per week. At baseline, the total and LDL-cholesterol levels of participants in the study ware 268 mg/dL (6.95 mmol/L and 180 mg/dL (4.68 mmol/L), respectively. After 4 weeks of enrollment in the program, there was a significant reduction in both total cholesterol and LDL-cholesterol to 240 mg/dL (6.30 mmol/L) and 161 mg/dL (4.16 mmol/L), respectively.

Additional confirmation and estimation of benefits associated with a reduction in serum cholesterol levels that are predictive of heart disease was provided using a computer model (Ref. 170). Subjects for the computer model system, included both men and women with blood cholesterol levels ranging from 200 mg/di (5.2 mol/L) to 300 mg/dL(7.8 mmol/L) at baseline. Data for the study incorporated updated estimates from both America (Framingham Heart Study) and Canada (Canadian Health Survey). Results suggested that, by reducing serum cholesterol levels by 5 to 33 percent, life expectancy could be lengthened by 0.03 to 3.16 years.

In summary, the updated literature review was consistent with and generally supported the tentative conclusions reached in the proposed rule (56 FR 60727 at 60735). That is,

diets low in saturated fat and cholesterol reduce blood cholesterol levels, particularly LDL-cholesterol levels.

C. Safety Issues

1. Trans-fatty Acids

One area identified in the proposed rule as a potential concern was the possibility of increased intake of *trans*-fatty acids as a result of changes in the fat composition of the U.S. food supply. One study that has been widely cited within the scientific-community is the study by Mensink and Katan (Ref. 95).

Studies that examined the effects of trans-fatty acids on serum cholesterol levels are limited and report conflicting results and conclusions. One *trans*- fatty acid study discussed and evaluated in Table 2 of the proposed rule (56 FR 60727 at. 60761, Ref. 95), reported that consumption of a diet enriched in *trans*-fatty acids (11 percent of total calories or 33 g/day) significantly increased total cholesterol and LDL-cholesterol and significantly reduced HDL-cholesterol levels in healthy subjects. The level of trans-fatty acids used was much higher than the level reported available for consumption by the U.S. population (3 to 4 percent of calories or 7 to 10 g/day).

In a recent study by Zock and Katan (Ref. 193), healthy, free-living, normolipidemic individuals (26 males and 30 females) consumed diets that compared the effect of C-18 fatty acids (saturated, trans-monoene, and unsaturated form) on serum lipids. Each diet, which did not differ in nutrient content, lasted for 3 weeks and was eaten as solid foods. In this multiple, cross-over design study, the *trans*-fatty acid level was set at 7.7 percent of total calories or 2.4 g/day. Both stearate and *trans*-fatty acid-enriched diets increased total cholesterol and LDL-cholesterol levels significantly, relative to the linoleate diet (a polyunsaturated fat). In addition, both stearate and *trans*-fatty acids significantly reduced. HDL-cholesterol relative to linoleate. Lower HDL-cholesterol levels were observed in 46 of 56 subjects on the *trans*-fatty acid enriched diet. The authors concluded that, if the data from this study are combined with those from the previous study (Refs. 95 and 193), the results suggested that for every 1 percent of energy derived from *trans*-fatty acids, LDL-cholesterol would increase by 1.2 mg/dL and HDL-cholesterol would be lowered by 0.6 mg/dL relative to an equivalent amount of oleic or linoleate. The authors concluded that the current U.S. trans- fatty acid consumption level of about 3 to 4 percent of total calories may increase LDL-cholesterol by 4 mg/dL and decrease of HDL-cholesterol by 2 mg/dL.

2. Unsaturated Fatty Acids

In the following group of studies, the effect of diets reduced in total fat, SFA, and cholesterol to levels suggested by national nutritional guidelines and health organizations was evaluated with respect to the possibility of increased intake of unsaturated fatty acids, especially PUFA's. This issue was raised in the proposal as a result of possible changes in the fat composition of the U.S. food supply (56 FR 60727 at 60735).

In a randomized, blinded, controlled dietary intervention study, the effect of diets enriched in vegetable oils on serum cholesterol levels in 31 free-living mildly hypercholesterolemic men (Ref. 192) was reported. Two conditions were examined: Test diets, in which the saturated fat content was 7 percent, (test) versus 15 percent in the control diets, were enriched in either MUFA (22 percent MUFA-test versus 14 percent-control) or PUFA (22 percent PUFA-test versus 9 percent PUFA-control) (refer to the Table). Total and LDL-cholesterol levels were reduced significantly by consumption of diets reduced in saturated fat and enriched (2.2 percent of calories) in either MUFA or PUFA (total cholesterol: -15 (PUFA) and -12 (MUFA) percent., and LDL-cholesterol: -20 (PUFA) and -12 (MUFA) percent. respectively).

3. PUFA-Enriched Diets Versus MUFA-Enriched Diets

A recent study by Mata et al. (Ref. 175) compared the long-term effects of PUFA-enriched diets versus MUFA-enriched diets, on blood cholesterol levels in 46 free-living, healthy men (mean age 33 years) and 32 women (mean age 42). The two diets were similar in all respects other than the content of the test unsaturated fatty acids (the PUFA-enriched diet content contained total fat 37 percent; SFA 12.5 percent; PUFA 13 percent; and MUFA-10 percent; while the MUFA-enriched diet had the same amount of total and saturated fat but 3.4 percent PUFA and 20 percent MUFA) (sea Table). This controlled, solid food study, was conducted in two phases: phase 1, PUFA-enriched diets (for 16 weeks) followed by a second phase, the MUFA-enriched diet, which lasted for 28 weeks. The MUFA-enriched-diet had no effect on blood total cholesterol in men but increased it in women. The MUFA-enriched diet increased HDL-cholesterol levels compared to the PUFA-enriched diet. HDL-cholesterol levels increased in both men (17 percent) and women (30 percent). No significant changes occurred in LDL-cholesterol or total triglycerides.

In summary, the updated literature review reveals relatively few new studies pertaining, to possible unintended safety effects from reducing dietary intakes of saturated fat and cholesterol. Possible adverse effects on LDL-cholesterol and HDL-cholesterol from the consumption of large quantities of *trans*-fatty acids are supported by recent scientific reports. Most results are consistent with those of earlier reviews (Refs. 20, 30 through 36, 135, 150, and 151) and with comments received in response to the proposed rule.

Overall, the updated literature review provided no convincing evidence to suggest that the agency's tentative conclusions as to the relationship of saturated fat and cholesterol to risk of heart disease, as described in the proposal, required modification.

IX. Conclusions

FDA has responded to all comments received in response to the proposed saturated fat and cholesterol and CHD health claim regulation. In addition, the agency has reviewed all additional scientific studies received in comments or independently identified The agency has determined that the new studies strengthen the tentative conclusions reached in the proposed regulation. After considering the comments and the new scientific studies, the agency concludes that there is significant scientific agreement based on the totality of publicly available scientific evidence that a claim that diets low in saturated fat and cholesterol may reduce the risk of CHD is supported by that evidence. Therefore, FDA is authorizing a claim.

The agency has decided that the regulations for the authorized health claims are most useful if they follow a consistent format and require only information that the agency considers essential. Therefore, the agency has made a number of editorial changes in the proposed codified material of the saturated fat and cholesterol and CHD health claim to make it more consistent with other authorized claims.

X. Environmental Impact

The agency has determined under 21 CFR25.24(a)(11)that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XI. Economic Impact

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

FDA has evaluated more than 300 comments that it received in response to the November 1991 RIA. FDA's discussion of these comments is contained in the agency's final RIA-published elsewhere in this issue of the **Federal Register**. In addition, FDA will prepare a final regulatory flexibility analysis (RFA) subsequent to the publication of the food labeling final rules. The final RFA will be placed on file with the Dockets Management Brands (HFA-4p5), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, and a notice will be published in the Federal Register announcing its availability.

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

XII. References

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List of Subjects in 21 CFR Part 101

Food Labeling, Reporting and recordkoeping requirements.

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

PART 101—FOOD LABELING

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

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

2. New § 101.75 is added to subpart E to read as follows:

§ 101.75 Health claims: dietary saturated fat and cholesterol risk of coronary heart disease.

(a) *Relationship between dietary saturated fat and cholesterol and risk of coronary heart disease.* (1) Cardiovascular disease means diseases of the heart and circulatory system. Coronary heart disease is the most common and serious form of cardiovascular disease and refers to diseases of the heart muscle and supporting blood vessels. High blood total- and low density lipoprotein (LDL)- cholesterol levels are major modifiable risk factors in the development of coronary heart disease. High coronary heart disease rates occur among people with high blood cholesterol levels of 240 milligrams/decaliter (mg/dL) (6.21 millimoles per liter (mmol/L)) or above and LDL-cholesterol levels of 160 mg/dL (4.13 mmol/L) or above. Borderline high risk blood cholesterol levels range from 200 to 239 mg/dL (5.17 to 6.18 mmol/L) and 130 to 159 mg/dL (3.36 to 4.11 mmol/L) of LDL-cholesterol. Dietary lipids (fats) include fatty acids and cholesterol. Total fat, commonly referred to as fat, is composed of saturated fat (fatty acids containing no double bonds), and monounsaturated and polyunsaturated fat (fatty acids containing one or more double bonds).

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

(b) *Significance of the relationship between dietary saturated fat and cholesterol and risk of coronary heart disease.* (1) Coronary heart disease is a major public health concern in the United States, primarily because it accounts for more deaths than any other disease or group of diseases. Early management of risk factors for coronary heart disease is a major public health goal that can assist in reducing risk of coronary heart disease. There is a continuum of mortality risk from coronary heart disease that increases with increasing levels of blood LDL-cholesterol. Individuals with high blood LDL-cholesterol are at greatest risk. A larger number of individuals with more moderately elevated cholesterol also have increased risk of coronary events;

such individuals comprise a substantial proportion of the adult U.S. population. The scientific evidence indicates that reducing saturated fat and cholesterol intakes lowers blood LDL-cholesterol and risk of heart disease in most individuals. There is also evidence that reducing saturated fat and cholesterol intakes in persons with blood cholesterol levels in the normal range also reduces risk of heart disease.

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

(3) Intakes of saturated fat exceed recommended levels in many people in the United States. Intakes of cholesterol are, on average, at or above recommended levels. One of the major public health recommendations relative to coronary heart disease risk is to consume less than 10 percent of calories from saturated fat, and an average of 30 percent or less of total calories from all fat. Recommended daily cholesterol intakes are 300 mg or less per day.

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

(2) Specific requirements. (i) *Nature of the claim*. A health claim associating diets low in saturated fat and cholesterol with reduced risk of coronary heart disease may be made on the label or labeling of a food described in paragraph (c)(2)(ii) of this section provided that:

(A) The claim states that diets low in saturated fat and cholesterol "may" or "might" reduce the risk of heart disease;

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

(C) In specifying the nutrient, the claim uses the terms "saturated fat" and "cholesterol" and lists both;

(D) The claim does not attribute any degree of risk reduction for coronary heart disease to diets low in dietary saturated fat and cholesterol; and

(E) The claim states that coronary heart disease risk depends on many factors.

(ii) *Nature of the food*. The food shall meet all of the nutrient content requirements of § 101.62 for a "'low saturated fat," "low cholesterol," and "low fat" food; except that fish and game meats (i.e., deer, bison, rabbit, quail, wild turkey, geese, and ostrich) may meet the requirements for "extra lean" in §101.62.

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

(2) The claim may indicate that the relationship of saturated fat and cholesterol to heart disease is through the intermediate link of "blood cholesterol" or "blood total- and LDL cholesterol."

(3) The claim may include information from paragraphs (a) and (b) of this section, which summarize the relationship between dietary saturated fat and cholesterol and risk of coronary heart disease, and the significance of the relationship.

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

(5) The claim may include information on the number of people in the United States who have coronary heart disease. The sources of this information shall be identified, and it shall be current information from the Rational Center for Health Statistics, the National Institutes of Health, or "Nutrition and Your Health: Dietary Guidelines for Americans," U.S. Department of Health and Human Services (DHHS) and U.S. Department of Agriculture (USUAL Government Printing Office.

(6) The claim may indicate that it is consistent with "Nutrition and your Health: Dietary Guidelines for Americans," DHHS and USDA. Government Printing Office.

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

(e) Model health claims. The following are model health claims that may be used in food labeling to describe the relationship between dietary saturated fat and cholesterol and risk of heart disease:

(1) While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease;

(2) Development of heart disease depends upon many factors, but its risk may be reduced by diets low in saturated fat and cholesterol and healthy lifestyles;

(3) Development of heart disease depends upon many factors, including a family history of the disease, high blood LDL-cholesterol, diabetes, high blood pressure, being overweight, cigarette smoking, lack of exercise, and the type of dietary pattern. A healthful diet low in saturated fat, total fat, and cholesterol, as part of a healthy lifestyle, may lower blood cholesterol levels and may reduce the risk of heart disease;

(4) Many factors, such as a family history of the disease, increased blood- and LDL-cholesterol levels, high blood pressure, cigarette smoking, diabetes, and being overweight, contribute to developing heart disease. A diet low in saturated fat, cholesterol, and total fat may help reduce the risk of heart disease; and

(5) Diets low in saturated fat, cholesterol, and total fat may reduce to risk of heart disease. Heart disease is dependent upon many factors, including diet, a family history of the disease, elevated blood LDL-cholesterol levels, and physical inactivity.

Dated: November 3, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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

BILLING CODE 4160-01-F

TABLE

Dietary Standard Fat and Cholesterol and Coronary Heart Disease

Study	Study Design	Subjects	Methods	Results	Comments
Nestol P. et al. (Ref. 177).	Double blind, controlled, cross-over clinical trial of free-living subjects. Purpose: comparison if diets differing in concentration of SFA and PUFA (edible oil blends, containing hydrogenated oils and therefore trans fatty acids) on blood lipid levels. Trans fatty acid content was 4% of total calories. Study site: Australia	Twenty-six mildly hypercholesterolemic free-living men (5 to 7.5 mmol/L or 193 to 290 mg/dL), ages 20 to 65 years.	Dietary instruction, food records for 3 consecutive days, total of 12 days. 14 weeks diet study: 2 weeks run-in; 4 weeks control diet and 4 weeks each test diet Composition of Diets: % of calories Control / Test 1 / Test 2 Fat 42 / 42 / 42 PUFA 6 / 10 / 11 MUFA 15 / 16 / 16 SFA 17 / 13 / 12 Chol (mg) 214 / 175 / 164 Test blend 1 contained 50% sunflower oil and a mixture of partially hydrogenated cottonseed and soybean oil. Test blend 2 contained 50% sunflower oil and partially hydrogenated canola and palm olein.	Total cholesterol (TC) and LDL-C were significantly reduced by consumption of diets containing oil blend 1 and 2 compared to controls. HDL-C and triglycerides (TG) were not significantly altered by consumption of test (oil blend diets) 1 and 2 compared to control diet. Results: (lipids in mg/dL) Control / Test 1 / Test 2 TC 221 / 216 / 212 LDL-C 154 / 150 / 147 HDL-C 42 / 42 / 42 When about 8% of energy from palmitic acid was exchanged for oleic acid, both LDL and HDL-cholesterol increased significantly. Therefore plamitic acid was either neutral or hypercholesterolemic dependent on the initial LDL receptor activity (subjects were hypercholesterolemic (>220 mg/dL) by malfunction in LDL-receptor activity).	Study suggests that edible oil blends that are lower in SFA (36 versus 21%) and higher in PUFA (21 versus 35%) than currently available in the market, can lower TC and LDL-C even when part of the diet in which fat is 42% of calories. Results of study were different than predicted by Keys equation. When trans fatty acid were treated as if they were SFA, then the Keys equation predicted closely the results observed.
Walden C et al. (Ref. 191)	Recruitment and design of dietary intervention study. Purpose: compare effectiveness of diets equivalent to NCEP Step I and Step II diets in lowering blood cholesterol on two different types of hyperlipidemia in free-living subjects. Study site: Washington State area.	320 hypercholesterolemic (HC) and 211 combined hyperlipidemia (CHL) men.	Initial dietary instruction provided, 8 weeks diet classes, 4 day food records maintained, evaluated at 6 month intervals. Four diet regiments compared: differing % fat, and amount of cholesterol. PUFA to SFA content held constant (ratio 1.0) % of Calories I / II / III / IV Fat 30 / 25 / 20 / 15 SFA 10 / 7 / 7 Chol (mg) 300 / 200 / 100 / 100	Out of 8,372 men screened for study, 47.7% were in the 60th percentile for elevated cholesterol and LDL-C, and elevated triglyceride (TG). Baseline lipid profiles for those classified as HC and CHL were similar. Fat was 36% of calories and cholesterol ranged from 279 to 316 mg/day in baseline diets.	Demonstrates the need for dietary intervention since a significant number of these industrial workers had elevated TC and LDL-C.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Bonanome A. et al (Ref. 159)	Self-controlled clinical trial 1 Italy in free-living subjects. Purpose: compare effects of carbohydrate and MUFA diets on blood cholesterol level. Clinical hospital out-patients.	NIDDM patients whose diabetes was under control. 10 men and 9 women, average age 55 years. Free-living	Dietary counseling, 2 months on each diet. Three phases: carbo-MUFA-carb: isocaloric diets; MUFA from olive oil. % of calories Fat: Carb 25, MUFA 40 MUFA: Carb 10, MUFA 25 PUFA: Carb 5, MUFA 5 Chol (mg): Carb <300, MUFA <300 Carb: Carb 60, MUFA 45	Baseline glucose, insulin and lipid parameters showed NIDDM under control. No statistically significant difference in TC, LDL-C or HDL-C found between carbo and MUFA enriched diets. Slight increase in TC and HDL on MUFA diet. Plasma LDL-C, TG and HDL-C did not change significantly by changing from one dietary phase to another. Results: serum lipids (mg/dL) TC: Carb 239, MUFA 251 LDL-C: Carb 163, MUFA 166 HDL-C: Carb 42, MUFA 51	Study suggests that it is possible to substitute SFA calories with either carbohydrate or MUFA and obtain similar results on blood cholesterol levels. This is expecially important for NIDDM patients, because they were still able to maintain gycemic control on either diet.
Denke M et al (Ref. 162)	Cross-over, controlled clinical trial. Purpose: compare effects on blood cholesterol of diets differing in type and amount of SFA. Study site: Texas Medical Center	Ten men, mean age 66 years, 5 of whom smoked, baseline TC 6 mmol/L (232 mg/dL); TG 1.5 mmol/L; free-living	Liquid diets: 3 weeks each diet. Cross-over 1 week ad libitum diet. Random order of diets. All diets: fat 40% of calories, 40% carbo., chol 120 ug/kcal, PUFA <8%. Fat: % SFA / % stearic Butter: 25 / 4 Beef: 18 / 7.6 Cocoa: 23 / 13 Olive: 8 / 1.2	High concentration of stearic in beef fat did not negate its cholesterol-raising properties. Cocoa butter not significantly less hypercholestrolemic than beef fat. Results: serum lipids (mg/dL) Butter: TC 219, LDL-C 164, HDL-C 34 Beef: TC 211, LDL-C 156, HDL-C 36 Cocoa: TC 198, LDL-C 147, HDL-C 34 Olive: TC 188, LDL-C 140, HDL-C 34	Possible differences due to liquid diet, comparisons to solid food diets would be helpful. The authors suggested that base line drops in TC and LDL-C (even on butter diets) was duet to regression toward mean and/or hospitalization.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Bierenbaum M. L. et al (Ref. 158)	Controlled clinical trial in free living subjects. Purpose: measure effects of canola oil (enriched in PUFA) on serum lipids. Study sites: New Jersey/New York, hospitals	Thiry-six free-living hypercholesterolemic and/or hypertriglyceridimic patients. Twelve men and 15 women, average age 60.7 years. Four had diabetes, 14 post-CVD event, 2 post-MI Baseline lipids (mg/dL): TC 254 LDL-C 173 HDL-C 47 TG 214	Dietary instruction. 4 months on diet. 24-hour food diary prior to and during study. Diet: % of calories Basal / Test Fat 39% / 39% SFA 19% / 30 ml/day MUFA 11% / canola oil PUFA 9% / exchanged Chol 390 (mg/day) / for basal dietary oil	Dietary adherence monitered by measuring w-3 fatty acid in RBC membrane before and after 4 months on diet. Both 18:3 (w-3) 22:6(w-3) significantly increased from 1.4 to 39.8% and 0.7 to 10.2% respectively, while 18.0 decreased from 25 to 3.2%. No significant changes in total chol, HDL-C, TG, or BP. LDL-C was lowered significantly by the PUFA enriched diet. Blood lipid results (mg/dL) TC 248 LDL-C 160 HDL-C 51 TG 226 Serum a-tocopherol and B-carotene significantly decreased and retinol unchanged after 4 months on diet. Bleeding times increased significantly.	Dietary data not adequately described. Two types of hyperlipidemic may respond to differently to dietary changes. Response not necessarily equivalent to normal subjects. Study suggests a need for increased supplementation of antioxidant vitamins when increasing concentration of PUFA in the diet. One subfraction of HDL (HDL-2) decreased on PUFA inriched diet.
Garcia P. A. et al (Ref. 168)	Cross-over, controlled clinical trial in free-living subjects. Random order of diet treatment sequences. Purpose: measure effects of diets differing in fatty acid composition (SFA and PUFA) on serum lipids. Study site: Iowa and Nebraska	Twenty women; 10 from Nebraska, 10 from Iowa; 5 were Chinese and 14 Caucasian; average age 23 years; free-living. Baseline lipids (mg/dL): CA / CH TC 154 / 166 LDL-C 86 / 97 HDL-C 44 / 47 CA = caucasian CH = chinese	Dietary records self recorded: 28-day/diet total 70-day study. 3 diets: self selected (SS), two experimental diets: US74 and modified fat (MOD). Meals provided and food records maintained through study for US74 and MOD diets. Test Diet Composition US74 / MOD Fat (%) 40% / 30% PUFA 4 / 10 MUFA 14 / 10 SFA 14 / 10 Chol(mg) 600 / 300	Chinese women had consistently higher TC, LDL-C, HDL-C and TG levels that Caucasian women regardless of diet selected. Caucasian women only showed significant decrease in TC, LDL-C, VLDL-C when effect of diet increased TC, VLDL-C in Chinese women compared to self selected diet. Cross over diet effect on HDL levels of both groups of women. Blood lipids (mg/dL) US74 / MOD CA CH / CA CH TC 163 195 / 139 159 LDL-C 89 104 / 75 85 HDL-C 46 51 / 44 49	Uneven numbers of subjects in each racial group. The Caucasian group from Iowa was significantly physically larger than the mixed racial group from Nebraska. Signifcant effects of experimental diets may have been masked by residual diet effects.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Wardlaw G. M. et al (Ref. 144)	Two-phase, randomized, blinded, free-living, controlled clinical trial. Purpose: measure effects of diets enriched in PUFA and MUFA, low in SFA on blood lipids while maintaining % energy from fat at 38%. Study site: Ohio.	Thirty-one men completed the study. One criteria for selection of subjects was blood chol >5.16 mmol/L (199 mg/dL). Average age of free-living subjects was 33 years.	Baseline (BL) diet 3 weeks (phase 1), Test diets Mono (enriched MUFA) and Poly (enriched in PUFA), 8 weeks each (phase 2). All meals provided for study. Diets Composition (% of Calories) BL / MONO / POLY Fat 39 / 40 / 39 SFA 15 / 7 / 7 MUFA 14 / 22 / 9 PUFA 9 / 11 / 22 Chol (mg) 360 / 320 / 320	TC fell from baseline significantly: -15% POLY and -9% MONO: LDL fell significantly from baseline by –20% POLY and –12% MONO enriched diets: apo B fell significantly from baseline by -21% POLY and –24% MONO enriched diets. Neither vegetable oil based diets resulted in a significant change in TG, HDL-C, HDL-2, or HDL-3, apo AI when compared baseline diet. Blood lipid results (mg/dL) BL / MUFA / PUFA TC 208 / 189 / 178 LDL-C 143 / 123 / 116 HDL-C 42 / 39 / 42	Results indicate that consumption of diets low in SFA reduces blood cholesterol. Study also suggests that diets enriched in UFA do not necessarily decrease blood levels of HDL and/or increase TG. Study showed that when dietary energy from fat is 39% of calories (therefore higher than recommended by public health authorities), but the SFA content of the diet is reduced, it is possible to still achieve a reduction in blood cholesterol levels.
Reaven P. et al (Ref. 181)	Controlled dietary intervention clinical trial in free-living subjects. Purpose: compare effect of diets enriched in MUFA (18:1) with PUFA (18:2) on blood cholesterol levels and oxidative potential on LDL-C. Random diet assignment Study site: California University	Nine healthy volunteers, age 18 to 43 years. Gender not stated. Baseline lipids (mg/dL): olea. / linolea. TC 166 / 147 LDL-C 96 / 69 HDL-C 46 / 62	Liquid diets (fat content less than 1%) to which test oils are added. Test oil one: Trisun 80 = >85% 18:1 (oleic acid). Test oil 2 sunflower oil, >60% 18:2 (linoleic acid). 5-week/diet. Diets enriched in (% of calories) Oleate / Linoleate Fat 39.2 / 39.2 SFA <2 / <4 MUFA 34 / 9.6 PUFA 6 / 27 Chol 0 / 0 Fatty acid content for sunflower oil was not given by authors, and was as estimated here by using data from another publication, in order to evaluate study results.	No significant decrease in TC or LDL-C by either diet. HDL-C decreased significantly in linoleate (PUFA) supplement Blood lipid results (mg/dL) oleate / linoleate TC 147 / 113 LDL-C 77 / 58 HDL-C 46 / 49 Other results: Antioxidant (vitamin E)conc not significantly reduced by either diet. The amount and rate of formation of conjugated dienes (measure of degree of unsaturation) greater in linoleate group. No significant increase in TBAR (a measure of oxidization in LDL-C). However, significant increase in LDL-C degradation (measure of atherscleratic potential) by macrophages in linoleate group.	Complete fatty acid analysis of oils used not provided in paper, especially important in case of Trisum 80. Preliminary study can not at this time apply results to general public health advise.

TABLE—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Cole T. G. et al (Ref. 161)	Dietary, clinical intervention trial. Purpose: effect of AHA Phase 3 diet (very low fat and cholesterol) diet on blood cholesterol levels Study site: Chicago	Nineteen free-living premenopausal women, mean age 32. Selection based on TC at or > than 50th percentile. Healthy subjects. Six women were classified as grossly obese by body mass index (BMI > 30). Mean BMI for all subjects 28.2. Baseline lipids (mmol/L & mg/dL) TC 5.24 205 LDL-C 3.45 133 HDL-C 1.36 52	Stabilization diet: 28 days on typical American diet. 5 months on AHA Phase 3 diet. % of calories AMER AHA 3 Fat 37 21.4 Carb 43.8 59.4 Prot 19.2 19.2 SFA 15.7 4.7 MUFA 11.7 6.4 PUFA 6.7 8.4 Chol 271 96 (mg/day) meals provided on site	TC, LDL-C, HDL-C and HDL-2 decreased when all women were considered as a group. HDL-3, TG and VLDL-TG increased when all women considered as a group. Blood lipid results (all subjects in mg/dL) AMER AHA 3 TC 202 189 LDL-C 133 121 HDL-C 52 49 When women were divided into 3 groups based on BMI, leanest women had a significant decrease in TC, LDL-C and HDL-C. Blood lipid (mg/dL) response grouped by BMI <24 <30 >30 TC 169 202 199 LDL-C 106 130 128 HDL-C 49 57 40 Moderately and grossly obese women were not nonresponders.	Results suggest that obesity, at least in women (n=6 BMI>30) had an influence on responsiveness to low-fat, low-cholesterol diet. Authors suggest that obese women may be carbohydrate-sensitive and therefore less responsive to low fat, low SFA diet.
Kwon, Jon-Sook et al (Ref. 172)	Controlled dietary, intervention study in free-living subjects. Purpose: study the effects of diets enriched in UFA from vegetable oils on platelet phospholipid (PL) fatty acid composition and function. Two phase diet design: phase 1, a 3-week baseline or control diet; followed by phase 2, an-8 week experimental diet. Study site: Ohio.	Thirty-four healthy males ages 21 to 50 years. All subjects had chol concentrations of 4.8 to 7.8 mmol/L (185 to 301 mg/dL) on self selected diet. All subjects consumed baseline diet. Sixteen assigned to diet enriched in PUFA and 14 assigned to diet enriched in MUFA.	Three diets: Baseline enriched in SFA, Canola enriched in MUFA and Safflower oil enriched in PUFA. Meals provided, eaten on site and dietitian monitored. % of Calories Base MUFA PUFA FAT 38.8 39.9 39.3 SFA 15.4 7.2 7.4 MUFA 13.8 22.8 8.1 PUFA 8.6 10.7 22.2	Compared to SFA enriched diet, platelet PL fatty acid composition was altered. MUFA enriched diet (canola) raised conc of oleic (MUFA) and linoleic (PUFA); there was a significant decrease in oleic and increase in linoleic with the PUFA enriched diet (safflower). Both vegetable oil diets produced increases in SFA (louric and palmitic), a decrease in stearic acid of PL fatty acids of platelet compared to SFA diet. Both vegetable oil diets significantly increased platelet aggregation time compared to platelet from SFA diet. Data: Diet Aggregation. MUFA PUFA SFA	Authors discussed the possible mechanism by which UFA from vegetable oils may platelet aggregation time. The authors suggest that vegetable oils: canola oil, may alter platelet aggregation by PG metabolism and membrane fluidity and safflower oil by membrane fluidity. The authors also suggested that the increased conc of 2 SFA (palmitic acid stearic) in PL of platelet may not be prothrombic.

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Study	Study Design	Subjects	Methods	Results	Comments
McMurry P. et al (Ref. 176)	Dietary intervention study. Purpose: to measure the effects of an *industrialized, western, or affluent* diet on blood lipids levels of subjects who normally consume low fat, low SFA high fiber diets, the Tarahumara Indians Two phase design: phase 1, 1 week traditional diet, followed by phase 2, 5 weeks on test diet. Study site: Chihuahua, Mexico	Tarahumara Indians (Mexico) 12 adults (18 to 35 years), 1 boy (12 years). Five women (3 lactating) and 8 men. Baseline TC 121 mg/dL. Free-living.	Tarahumara diet and test or westernized diet provided. Diet Composition Tarahumara "Western" Energy (kcal) 2,700 4,100 % of calories FAT 20 43 MUFA 10 19 PUFA 4 4 SFA 7 21 Dietary fiber 102 33 Chol (mg) <50 1,020	TC, LDL-C HDL-C and TG levels increased significantly in all subjects. Blood lipid results (mg/dL) Tarahumara "Western" TC 121 162 LDL-C 72 100 HDL-C 32 42 Increase in TC occurred very rapidly in response to the western diet. Women has a non-significantly higher increase in TC than men. Lactating women responded similar to non-lactating women. Adolescent boy had the highest initial and final TC level.	Test diet was 151 to 186% of estimated eucaloric needs. Response could be due to load response. Study complicated by large number of subgroups. Large percentage of SFA (21%) content in diet compared to US.
Rassias G. et al (Ref. 180)	Controlled, cross-over design dietary intervention clinical trial in free-living subjects. Purpose: compare the effects of diets supplemented with linoleic and SFA on serum lipids. Random order of diets; no wash-out between diets. 2 weeks on base line diet and 3 weeks on test diets Study site: Australia	Twelve mildly hypercholesterolemic individuals (five men seven women, ages 27 to 74 years. (5 subjects 20 to 30 and 7, 30 to 74 years.) Baseline blood lipids mmol/L and (mg/dL) TC BMI Men 6.22 (240) 43 Women 6.17 (238) 56	Supplements provided in liquid form. 3-day food records maintained for each test period. Supplements-SFA and PUFA (linoleic) Diet Comparison (% of calories) BL SFA PUFA FAT 35.6 48.0 46.6 SFA 13.2 30.5 10.8 MUFA 11.6 9.2 10.8 PUFA 7.9 6.1 22.7	The linoleic-enriched diet significantly lowered TC 0.5 mmol/L compared to basal diet and 1.0 mmol/L compared to SFA-enriched diet. This decrease in TC occurred without a reduction in SFA content or replacement of SFA with PUFA. Comparing basal diet to PUFA enriched diet: the linoleic enriched diet did not decrease HDL-C levels. Data blood lipids mmol/L and (mg/dL) BL SFA PUFA TC 6.0(233) 6.5(251) 5.6(215) LDL 4.4(170) 4.6(177) 3.8(145) HDL 1.3(51) 1.6(63) 1.4(56)	Results suggest more alternatives in choosing nutrient substitutes for dietary saturated fat. Diets significantly lower in total of SFA but enriched in PUFA such as linoleic may also reduce TC levels.

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Study	Study Design	Subjects	Methods	Results	Comments
Stacpoole P. W. et al (Ref. 184)	Dietary intervention clinical trial. Purpose: investigate the mechanism of cholesterol lowering action induced by high carbohydrate, very low fat feeding as reflected in changes in VLDL and LDL metabolism. Two phase dietary intervention: 1 phase basal diet for 1 month; wash-out 3 months, test diet 1 month. Study site: Shand Hospital, Florida.	Four healthy controls(N=normal), four familial hypercholesterolemia (FH)-heterozygous, and one FH homozygous patients. Healthy volunteers 33 to 58 years, FH patients 20 to 65 years. Baseline blood lipids (mg/dL) N FH TC 186 460 LDL-C 101 400 HDL-C 47 51	Whole body cholesterol balance and tracer kinetics methods used. Lipid profile, fecal sterol balance, apo B synthesis and metabolism. Compartmental analysis. Diet provided and supervised. Basal diet (BL) solid food; test diet, continuous nasal gastric infusion. Diet composition (% of calories) BL Carb Carb 45% 90.5% Fat 40% 8.2% Prot 15% 1.3% P/S 1.0 Linoleic Chol (mg) 100 none	Both normal controls and FH patients total cholesterol and LDL-C decreased significantly (mean difference 43 mg/dl and 123 mg/dl respectively) by consumption of high carbohydrate diet. HDL-C decreased non-significantly in all subjects, serum TG increased significantly. Blood lipid data BL Carb N FH N FH TC 186 460 138 338 LDL-C 101 400 62 270 HDL-C 47 51 32 36 Other data: Decrease in fecal cholesterol and bile acid production and decrease in whole body cholesterol formation in all subjects. Cholesterol synthesis fell 24% (8.4 to 6.4 mg/kg per day)in controls and 58% (11.4 to 4.8 mg/kg/day) in FH subjects. Consumption of carbohydrate diet stimulated LDL-apo B clearance in all subjects.	As authors point out, there are still uncertainties whether frequent or continuous feeding of liquid formula containing mostly glucose is more effective in lowering total cholesterol than solid diets containing a variety of carbohydrates. Another possible issue is the safety of high carbohydrate extremely low fat diets as well as safety of liquid formula diets. For the above reasons application of study results, other than for suggestions of mechanism for control for cholesterol homeiostasis, is not applicable to general public.

Study	Study Design	Subjects	Methods	Results	Comments
Dobs A. S. et al (Ref. 164)	Prospective, random, double blind, pravastatin and placebo- controlled clinical trial. Purpose: evaluation of drug and long-term dietary compliance, nutritional adequacy with a lipid-lowering diet. Subjects were randomly assigned to placebo or pravastatin (5, 10, 20 mg/day) for 12 weeks all subjects were placed on open-label pravastatin for the remaining 36 weeks. Multicenter trial Study sites: seven lipid treatment center in the United States	Two hundred and seventy-two adults: 206 men and 66 women; mean age 50 years (21 to 70 years); hypercholesterolemic (85th percentile) patients (76% men) aged.	Each subject had 6 weeks of dietary counseling. Basal diet (lipid lowering) for > 6 weeks. Seven, 1-day diet records kept for 1 year.	272 patients selected had elevated serum LDL after greater than 6 weeks of dietary counseling and as such were considered unresponsive to a diet lower in fat, SFA and cholesterol. Blood lipid data (mmol/L and mg/dL): Total cholesterol <1 week 8 weeks 48 weeks Men 4.6(176) 5.0(190) 92.9(186) Women 4.0(176) 3.1(116) 3.6(137) data from all subjects pooled: LDL-C decreased from 193 down to 150 mg/dL). Report given on 23 participants from John Hopkins in which pravastatin reduced TC 23% [about 265 down to 200 mg/dL] and LDL-C 30% [about 210 down to 150 mg/dL] over the year. TG and HDL did not change. Dietary compliance and evaluation given. 55% of men in study completed 7 diet records for 1 year. For both men and women the percentage of calories from total fat was (30%), SFA (8%), PUFA (9%) and MUFA (10%). Approximately two-thirds of participants ingested less than 67% of RDA of some essential mineral and vitamin nutrients.	Intervention with lipid lowering drug did not alter dietary compliance. Patients adhering to lipid lowering diets in which the fat content was similar to that recommended for general population (30% of calories), appeared to contain inadequate amounts of several essential nutrients (folic acid, vitamin B-6, vitamin D, calcium and Zn. Compared to general population the nutrient amounts were greater for zinc and calcium but less for vitamin B-6 and folic acid than that found in general population. In men the diet was inadequate in folic acid and zinc. Lipid lowering diet may be inadequate in several micronutrient. Other studies have however found these diets provide adequate amounts of these nutrients.
Todesco T. et al (Ref. 185)	Cross-over, random dietary intervention clinical trial in free-living subjects.Purpose: to test the effects of supplementation of short chain fatty acid (SCFA) on blood glucose and cholesterol levels 2 phases: control and test diet. Random order of diets. Study site: medical school and hospital, Italy.	Six healthy volunteers, mean age 32 years; 3 males and 3 females; normal blood glucose and cholesterol levels. Baseline lipid data mmol/L mg/dL TC 5.0 193 LDL 3.2 123 HDL 1.25 48	Each diet period was 1 week including test diet. Diets similar except for supplementation of bread with propionate (9.9 g/150 g of carbohydrate). Maintained diet records day 0 and day 3 of each study. Diet composition (% of calories) Control Propionate Carb 52 53 Prot 17 18 Fat 29 29.5 Fiber 19.2 19.6	A significant decrease in blood glucose response was observed with use of propionate-supplemented bread compared to control bread. No signifcant changes were observed in total cholesterol, LDL-C, HDL-C or triglycerides. 5 subjects however showed a reduced level of HDL-C and increased triglycerides with propionate-supplemented bread use. Data mmol/L (mg/dL) Control Propionate TC 5.0 (193) 4.6 (185) LDL-C 3.2 (123) 2.8 (77) HDL-C 1.3 (50) 1.1 (42) TG 1.3 1.8	Short dietary test period, non-steady state conditions, no wash-out between diets. No indication of other confounders for glucose or lipid response (concentration of PUFA, MUFA, SFA or cholesterol). Does not confirm previous reports which suggest SCFA decrease total cholesterol by inhibiting HMGCoA reductase (or the synthesis of cholesterol).

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Study	Study Design	Subjects	Methods	Results	Comments
Ullman D. et al (Ref. 186)	Metabolic ward, dietary intervention clinical trial in free-living subjects. Purpose: First: to determine if carbohydrate-induced hypertriglyceridemia is avoided with 10-day phase in of 65% carbohydrate and 20% fat diet. Second: to determine if hypertriglyceridemia can be induced by an acute challenge of same diet. Study site: Oregon	Eight healthy nondiabetic adults (two women, six men) mean age 51. Mean Baseline blood lipid (mg/dL) TC 228 LDL-C 147 HDL-C 44 TG 254	Meals provided and compliance observed. Each diet period lasted 10 days. Study 1. Baseline (American) diet. Test diets increased in carbohydrate (65%) while decreasing in fat (20%). Study 2. (American) diet followed by acute 4 diet. Study 1 data (mg/dL) Amer 1 2 3 4 Carb 45 50 55 60 65 Prot 15 15 15 15 15 Fat 40 35 30 25 20 SFA 15 11 8 6 5 PUFA 6 8 8 8 8 MUFA 19 16 14 11 7 Chol 179 143 107 71 36	Study 1. Triglyceride or VLDL-TG did not significantly increase when carbohydrate concentration of diet was gradually phased in. TC was reduced significantly by phase 3 and phase 4. LDL-C was significanlty reduced at all phases. HDL-C was significantly reduced at phase 4 of the diet. Study 1 data (mg/dL) Amer 1 2 3 4 TC 232 223 216 209 198 LDL-C 161 144 141 134 126 HDL-C 43 41 44 42 36 TG 213 232 237 230 230 Study 2. An acute switch to high carbohydrate diet significanlty increased both TG and VLDL-TG in 6 of 8 patients. Study 2 data (mg/dL) Amer 65% Carb TC 243 233 LDL-C 174 143 HDL-C 43 41 TG 204 296	At least in some people, a gradual approach of phased increase in carbohydrate as replacement of calories from SFA, total fat and cholesterol may allow for better control of hypertriglyceridemia than previously reported.

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Study	Study Design	Subjects	Methods	Results	Comments
Bae, C-Y et al (Ref. 154)	Clinical dietary intervention in free-living subjects. Purpose: to determine the effectiveness of American Heart Association Step 1 Diet (% of calories-fat 30% or less, SFA 10% or less and cholesterol less than 300 mg/day in lowering blood cholesterol. Study site: Minnesota Hospital and Medical Center	Eighty-seven (49 men and 38 women) completed the study. Mean age 50.1 years. Baseline lipid data: TC 243 mg/dl; LDL-C 169 mg/dl.	Dietitian instructed and followups. Food records maintained. Analysis of 4-day food records every 6 weeks. Blood lipid analysis at 6, 12 and 18 weeks. Diet Composition at Baseline (% of calories) Fat 31.6 SFA 10.6 PUFA 6.8 MUFA 11.5 Carbo 50 Prot 16.8 Chol (mg/d) 232 Fiber-soluble 5.9 Calories 1,975	Modest but significant decreases in TC (-2.6%) and LDL-C (-3.5%) were observed at 6 weeks. No further reduction in TC or LDL-C were found at 12 or 18 weeks. By 18 weeks, TC and LDL-C levels showed a tendency to return to and even exceed baseline levels. Small increase in HDL-C (2.1%) and TG (3.8%) at 18 weeks. Blood lipid data in mg/dL at (6 weeks) and (18 weeks) BL AHA(6) AHA(18) TC 242 235 245 LDL-C 169 163 170 HDL-C 49 49 50 Diet results: 1. total dietary fat decreased at 6, 12 and 18 weeks (minus 2.7, 2, and 2.4% respectively).2. SFA and cholesterol consumption decreased also at 6, 12 and 18 weeks for SFA(minus –1.6, -1.5, and –2.4) and –46% and –50% for cholesterol at 12 and 18 weeks.	The AHA Step 1 diet was not effective in improving plasma lipids of these subjects. This may be due to fact that most participants had already achieved a low level of SFA and cholesterol intake at baseline. All participants knew thy were hypercholesterolemic prior to the study and were already following a self developed diet. Those subjects who responded the best were older, had higher LDL-C levels and had higher intake of total and PUFA at baseline.
Groth K et al (Ref. 196)	Clinical intervention by dietary instruction. Purpose: to evaluate the effectiveness of dietician instruction on reduction of blood cholesterol levels. Study site: Spokane Washington	Thirty women and 19 men, mean age 55 years. Mean baseline blood lipids: TC 6.95 mmol/L (268 mg/dL) LDL-C 4.68 mmol/L (174 mg/dL).	Four consecutive classes, 2 1/2 hr per/week. Class topics: (1) CHD the disease; (2) meal preparation; (3) fat definition and properties of specific foods; and (4) healthy food choices.Blood cholesterol levels determined prior to and after dietary instruction. Dietary instructional recommendations: total fat 20% of energy, cholesterol 100 mg/day, soluble fiber 50 g/day. Food recommendations few or lean cuts of meat, few or no dairy products, vegetables, whole grain products. Diet composition:	A significant reduction in TC and LDL-cholesterol before end last class (week 4). Reduction in TC and LDL-C was maintained 1 year after instruction. Blood lipid data: mmol/L (mg/dL) Pre 4 week 1 year TC 6.9(266) 6.3(243) 6.2(249) LDL 4.7(177) 4.2(162) 4.4(170) HDL 1.3 (50) 1.2(46) 1.3(50)	The measure of understanding of the study is evident by helping individuals realize an immediate (4 weeks) and sustained reduction in blood cholesterol levels (1 year). Study suggests that once dietary recommendations are understood, changes will be maintained. Nutritional instruction, therefore, could be instrumental in reducing blood cholesterol levels in the general population.

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Study	Study Design	Subjects	Methods	Results	Comments
Maron D. U. et al (Ref. 174)	Cross-sectional study. Purpose: Evaluate the effect of diet (SFA) on insulin levels in nondiabetic (obese) men with heart disease. Study Site: Stanford University	Two hundred and fifteen nondiabetic free-living men, 32 to 74 years with angiographically proven coronary artery disease (CAD). Baseline lipids mmol/L (mg/dL) TC 4.4 (170) LDL 2.8 (108) HLD 1.3 (50) other: BMI 26.7	4-day food records and physical activity records maintained (4 years). Index of obesity: BMI; change in BMI, and waist to hip ratio (WHR). Fasted and response glucose and insulin levels measured. Diet Composition (% of calories) Total Fat 32 SFA 10 MUFA 12 PUFA 7.5 Chol 279 (mg/day)	SFA and cholesterol correlated positively with all three indexes of obesity and with fasted and insulin response. Data for correlation of diet and response in various indexes: SFA Chol BMI 0.18 0.16 change in BMI 0.23 0.18 Waist/hip 0.21 0.22 Fast insulin 0.26 0.23 Insulin response 0.17 0.21 Carbohydrate consumption correlated negatively with all measures of obesity and with both measures of insulin. Multivarient analysis showed that SFA, MUFA and cholesterol, positively and significantly correlated with fasting insulin	Limitation of study: dietary data self reported. Study demonstrated that SFA consumption is positively related to insulin concentration independently of obesity in nondiabetic men with heart disease.
Vorster N. H. et al (Ref. 190)	Dietary intervention study. Random and controlled. Purpose: measure effect of 3, 7, or 14 eggs per week on serum lipid levels in subjects who followed a Western diet. Study site: South Africa	Seventy 18 to 19 year-old healthy male university students. Free-living subjects Baseline lipids mmol/L (mg/dL) TC 4.4 (170) LDL-C 2.8 (108) HDL-C 1.3 (50) other: BMI 22.3, nonsmokers	All subjects consumed baseline diet containing three egg/week for 3 months. One group continued this diet for additional 5 months and remainder either consumed 7 eggs or 14 eggs/week for 5 months. Diet composition Run-in Experimental Cal 3190-3429 3238-3548 Fat% 38-40 39-41 P/S .7-.8 .7-.8 Chol 3.80 403, 556, or 800 (mg) Fatty acids c16:0 22.5 mg same c18:0 12.4 c18:1 14.5 c18:2 32 c20.4 .26 Group 1 = 3 egg/week Group 2 = 7 egg/week Group 3 = 14 egg/week	All subjects at steady state due to consumption of baseline diet for 3 months as determined by multiple blood lipid analysis over 3 month period. Only small differences within groups and no significant differences in total cholesterol, LDL-cholesterol or triglycerides between groups. Group 3 (14 egg/week) had high creatine value (119 versus 86 umol/L). Group 3 had significantly higher total protein, total phospholipids and arachidonic acid. Blood lipid data at 7 months mmol/L (mg/dL) Group 1 2 3 TC 4.3(162) 4.7(175) 4.3(160) LDL 2.6(98) 2.8(104) 2.6(97) HDL 1.2(45) 1.3(48) 1.2(45) There was a significant increase in with in all subjects (4.6 kg from baseline).	Egg intake in the range consumed did not increase blood cholesterol levels in self selected diet. Authors suggested several reasons for the above results such as a high fat diet with a, relatively low P/S ratio may cancel effects of additional cholesterol, second that there was a metabolic adaptation to compensate for dietary Chol decrease in Chol synthesis or increase in Chol elimination and third that the phospholipids content may be hypeocholesterolemic effect of added cholesterol.

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Study	Study Design	Subjects	Methods	Results	Comments
Grover S. A. et al (Ref. 170)	CHD primary prevention computer model to estimate lifetime benefit of risk factor modification. Purpose: To evaluate lifetime benefits of reducing total cholesterol to prevent CHD through dietary modification or medical intervention. Study site: Canada	Men and women, age 35 to 65 years of age, free of CHD. Blood cholesterol levels at baseline range 5.2 to 7.8 mmol/L or (200-low risk to 300 mg/dL-high risk) with and without additional CHD risk factor.	Computer model based on Framingham Heart Study, Canada Health Survey Data. Program estimate average expectancy associated with modifying one or more CHD risk factors. Into model following factors are incorporated: age, sex, diastolic blood pressure, total cholesterol, left ventricular hypertrophy glucose intolerance and cigarette smoking. Adjustments also made for HDL using gender specific HDL modification for men and women.	Ability to forecast lifetime benefits depends on baseline levels, age, sex, and presence and absence of other risk factors. Reducing serum cholesterol levels 5 to 33% increases the average life expectancy 0.03 year or 11 days to 3.16 years. The average onset of symptomatic CHD would be delayed by 0.06 or 22 days to 4.98 years. Among 35 year old men and women, without other risk factors, reducing cholesterol from 300 to 200 mg/dL with diet or medication would increase life expectancy 1.64 year (men) and 0.98 year (women).	Computer model used is based on relatively short term clinical data- 5 to 10 year to predict lifetime benefits. Wide variation in results from reduction of blood cholesterol in men and women of various ages. Results similar to other models used to estimate benefit from lowering blood cholesterol. For example Taylor made: a 6.7% decline in total cholesterol increased life expectancy 3 days to 3 months for low-risk men and women age 20 to 60 years.
Ekstedt B. et al (Ref. 165)	Diet and exercise intervention study. Controlled study in free- living subjects. Purpose: to determine the effect of low calorie, fat, and cholesterol diet on blood cholesterol and triglyceride levels. Study site: Sweden	Seven healthy males, age 21 to 37 years. Nonsmokers. Study included statement that subjects had normal cholesterol and triglyceride levels but blood lipid data not provided.	Stabilization diet (fat 26 to 30% of calories) and exercise (run 5 to 10 km, 2 to 4 times per week) for 1 month prior to study. Four different diets compared; 8 days each diet (solid food), one test per year, while cross country skiing 160 Km. Low calorie (Lca); High fat and high chol (HF/HC); high chol (HC) Std Lca HF/HC HC Cal 3800 2399 3800 3800 Fat (%) 26 21 52 29 Chol (mg) 260 110 480 410 carb (%) 57 60 34 56	A significant decrease in both total cholesterol and LDL-C by consumption of each of the test diets compared to levels at baseline. No significant change in HDL-C with standard or low energy diet. Significant increase in HDL-C with high fat/high cholesterol diet (19%) and high cholesterol diet (30%). Serum triglyceride decreased by more than 30% but no difference due to diet. Blood lipid data (actual values not provided); data presented as percent increase or decrease: Std Lca HF/HC HC TC -26 -35 -20 -31 LDL -38 -50 -41 -50 HDL 6 8 19 30 Body weight decreased significantly on low calories diet (3 kg).	Other results not shown in table were: heavy exercise, irrespective of fat, calorie, or cholesterol content of diet, decreased LDL-C levels in healthy men. Loss in short term body weight did not increase cholesterol lowering effect of low calorie, low fat and cholesterol diet. Short term heavy physical activity had stronger influence on blood cholesterol levels, than did fat or cholesterol content of diet. Large variance in triglyceride levels among individuals. Can only apply results to short term heavy exercise diet and not moderate exercise and diet effects as may be common in general public.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Kok F. J. et al (Ref. 171)	Case-control study conducted 1986 to 1987. Purpose: to determine the levels of a trace element, antioxidant and PUFA levels in patients with atherosclerosis. Study site: Netherlands	Ninety-one CHD (cases) and 72 control male subjects, average age 53 years. Other confounders-proportion: alcohol (65%), smoke (28%), hypertension (35%), MI (35% in cases and 15% in controls). All subjects has coronary angiography. Stenosis in at least one coronary vessel: case subjects >85% and < 50% of controls.	Plasma selenium measured by neutron activation; tocopherol by high pressure liquid chronography; gas chromatography of methyl ester derivative of lipid extract of plasma PUFA.	Cases, compared to controls had significantly high levels of total cholesterol and LDL-cholesterol and lower levels of diastolic blood pressure and HDL-cholesterol. Plasma selenium was significantly lower in cases compared to controls. No significant differences in tocopherol or PUFA's. In subgroup of case where tocopherol is low (less than 1452 ug/dL), there is a corresponding significant lower ratio of selenium/PUFA.	Dietary history, which could impact on these results, was not provided in study. Study lacks a control group which had no previous history of or who had no MI or atherosclerosis. Also subjects had many other risk factors which may relate to the results i.e., smoking and not directly to atherosclerosis. The reason for evaluating the study was because of safety concerns with proposed changes dietary composition due to a decrease in SFA consumption and replacement with other nutrients such as PUFA and micronutrient status (such as antioxidants) have been expressed. Some previous reports suggested that selenium was significantly lower in acute MI or those who died from CVD.
Shea S. et al (Ref. 183)	Longitudinal , survey. Purpose: survey of Hispanic preschool children in New York, measurements include serum lipids, dietary index and body mass index (BMI).	One hundred and eight healthy (57 boys and 51 girls) Hispanic children, average age 4.5 years. Mean serum total cholesterol (TC) for 108 children was 158 mg/dL and LDL-cholesterol was 97 mg/dL.	Four 24-hour dietary record, 3 months apart. Two Willett semiquantitative food frequency questionnaires approximately 6 months apart.	Boys had slightly higher serum TC and LDL-cholesterol than the total group or the girls. Children in the highest tertile of total fat consumption (36.2% of total calories) compared to the lowest tertile (30.2% of calories) had significantly higher TC and LDL-cholesterol Furthermore, children in the highest tertile of SFA consumption (14.6% of calories) compared to lowest tertile (11.2% of calories) had significantly higher TC and LDL-cholesterol levels. Blood lipid data (mg/dL): Nutr. SFA Tertiles 1st 2nd 3rd TC 152 152 172 LDL-C 92 91 108 Nutr. TF (total fat) TC 154 151 171 LDL-C 93 90 108	Findings suggest that dietary fat, particularly SFA, is increases blood cholesterol, especially LDL-Chol in preschool children. Correlation R^2 TC LDL-C SFA 0.12 0.16 TF 0.08 0.10 Data adjusted in multiple linear regression models for caloric intake, age, sex, and body mass index.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Prewitt T. E., et al (Ref. 178)	Controlled clinical trial, diet intervention in free-living subjects. Purpose: to compare effects of high (37% of calories) diet on a. insulin like growth factor and b. blood cholesterol levels Study site: Chicago, IL.	Eighteen healthy premenopausal women, mean age 32 years. Subjects had higher than average levels of blood cholesterol (50th) percentile. Baseline blood lipid data other than range notated above was not provided in the paper. Other: mean BMI 30; n=12 BMI 23; n=6 BMI 38.4.	All subjects consumed the 37% fat diet for 4 weeks, followed by 20 weeks of the 20% fat diet. Diet composition (% of calories) High fat Low fat Fat 37% 20% P/S 0.5 1.8 Chol 266 94 (mg/d) Meals provided and monitored on site. Absolute amount of SFA and PUFA dietary data not provided in study; no data on MUFA content provided.	When all subjects were considered, total cholesterol (TC) and LDL-cholesterol tended to decrease by consumption of low fat, low cholesterol diet Consumption of low fat diet by the obese group, decreased TC and LDL-cholesterol. Blood lipid data: Entire group versus Obese (mg/dL) 37% 20% 37% 20% TC 200 185 205 193 LDL 127 120 143 127 HDL 46 50 40 41 No relationship was observed between BMI and TC or LDL-cholesterol when all subjects were considered together or divided into normal weight or obese groups.	There was no run-in or diet stabilization period. The study did not use a wash-out period between diets or alternatively use cross over design. In premenopausal, obese women consumption of a diet in which fat was 20% of calories and 94 mg/day reduced TC and LDL-cholesterol. Variance in absolute amounts of PUFA, SFA, MUFA complicates interpretation and applicability of results to general public or a subpopulation.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Berlin E. et al (Ref. 157)	Clinical trial, dietary intervention, free-living, controlled, randomized study. Purpose: To compare the effects of high fat diet (40% of calories) and low fat diet (20% of calories), on blood cholesterol levels and lipoprotein fluidity in premenopausal women. Diets also varied in amount of PUFA and SFA. Study site: BHNRC, Beltsville Maryland.	Thirty-seven healthy women between 20 and 40 years of age selected, 31 finished the study.	Free choice dietary period for one menstrual cycle. All women were then placed on high fat diet for 4 months (4 menstrual cycles) and then switched to low fat diet for 4 months. Food was provided, eaten on site or prepared for home consumption. Approximately 2,200 kcal per day. Diet composition data (% of energy): Nutrient and diet intervention groups 1 2 3 4 Carb 45 45 64 64 Fat 39 39 19 19 Chol 374 289 230 199 (mg) SFA 44 27 21 12 (g) C18:1 30 33 15 17 (g) C18:2 15 26 7 13 (g) fluidity measured by fluorescence anisotropies using the probe 1, 6 diphenyl 1,3,5 hexatriene (DPH).	Plasma cholesterol levels were lower during luteal phase of menstrual cycle regardless of diet. Blood total cholesterol data (mg/dL): Diet groups 1 2 3 4 follicle 160 152 157 154 Leuteal 148 140 152 149 in general low-fat, and higher portion of PUFA in the diet increased lipoprotein fluidity. Fluidity of VLDL was related to oleate and linoleate. Fluidity of LDL and HDL, however, showed an inverse relationship to oleate and linoleate content.	It is difficult to evaluate study based on P/S ratio, without grams or percent of SFA, PUFA, and MUFA in the diet. It is possible that the SFA content of the diet was the same throughout the study. This was not the case in this study as shown by composition in g of SFA content. No consistent relationship emerged from the study to indicate that lipoprotein fatty acid content determined either LDL-C or HDL-C fluidity. The dietary cholesterol content was more significant than fatty acid content in determining LDL fluidity. This result would suggest another important role of dietary cholesterol separate from its effect on blood cholesterol levels. Changes in fluidity of lipoprotein particles may in turn alter their interaction with receptors and therefore alter the fate of blood cholesterol levels

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Bazzarre T. L. et al (Ref. 155)	Cross-sectional Purpose: to examine the relationship of several cardiovascular disease risk factors (CDRF) such as blood pressure (BP), total cholesterol (TC), HDL-C, BNI and percent of fat with daily energy intakes (EI) and daily energy expenditure (EE). Study site: North Carolina	Farmers and farm wives. 84 men (mean age 53) 74 women (mean age 51). BMI for men was 62 and 43 for women.	Dietary data and activity records collected for 4 days. Subjects were instructed to maintain their normal diet and activities. No dietary composition provided in the study.	For both males and females, at every age group, energy expenditure (EE) was greater than energy intake (EI). Mean EI and EE were statistically less from females than for males. Mean systolic BP, diastolic BP, TC, HDL-C were within normal limits. Mean TC, HDL-C and diastolic BP was slightly higher in females than in males. Blood lipid data mmol/L (mg/dL) Males / Females TC 5.4(206) / 5.45(210) LDL 3.98(154) / 3.87(149) HDL 1.36(52) / 1.58(61) When EI compared to EE, farm men consumed and expended more energy than farm women. Energy data: Males / Females EI 2413 / 1761 EE 4300 / 2919 Balance (EI-EE) -1886 / -1158	EE obtained from a reliable activity record may be a more practical tool for assessing the possible relationship of energy metabolism to CHD risk factors such as total and LDL cholesterol. Males who expend energy (exercise) may reduce risk of CHD.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Demacker P. N. M. et al (Ref. 163)	Dietary intervention study. Cross-over design, in free-living subjects. Purpose: To compare the effect to two diets: one enriched in SFA and the other enriched in PUFA on postprandial lipoprotein metabolism Study site: Netherlands	Twelve normalipidaemic subjects (six males and six females), ages 21 to 26 years. Subjects had fixed pattern of daily activities, none smoked. Other: mean BMI was 22.	Subjects consumed each test diet 9 days with a 4-week wash-out with habitual diet. Lunch was prepared in hospital kitchen. Meals consumed at fixed time intervals. Dietary instruction was given and dietary records maintained for breakfast and dinner meals. Rate of absorption of retinyl palmitate was used as a marker to measure rate of fat absorption was added to lunch meal on day 9 of the study. Diets: contained 2,400 kcal; fat 36.5% and Carbo 47.5% of calories; and Chol 294 mg/day. [% of calories – diets:] SFA 21 10 MUFA 12 9 PUFA 3 18	Consumption of the PUFA enriched diet resulted in a significant decrease in TC and LDL-C compared to SFA enriched diet. HDL-C was not significantly altered by diet. Blood lipid data (mg/dL) SFA PUFA TC 118 108 LDL-C 71 59 HDL-C 38 36 Other results: There was a 43% decrease in chylomicron and their ruminants as well as a 20% decrease in VLDL due to consumption of the PUFA enriched diet. Chylomicron remnants wer 43% more rapidly removed on diet rich in PUFA compared to diet rich in SFA. Since the rate of absorption is the same, an increase in the rate of clearance of triglyceride and cholesterol rich particles may explain the significant decrease in blood levels of these lipoprotein particles by PUFA-enriched diet.	Because of the short duration of the study (9 days), applicable results refer to short half-lived lipoprotein particles [chylomicron, VLDL and their remnants]. Under these circumstances cannot conclude whether or not the PUFA enriched diet altered the level of HDL. Second, the PUFA enriched diet was also reduced in SFA (about 10% of calories). This decrease in SFA content may account for decrease in TC and LDL-C observed. Thus added PUFA when substituted of SFA did not negate the cholesterol lowering effect of decreasing the SFA content of the diet. If future studies support these results such that a PUFA enriched diet increases the rats of clearance for chylomicron remnants, this could suggest a decrease in a lipoprotein particle of atherogenic potential.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Seidell, J. C. et al (Ref. 182)	Cross-sectional survey Purpose: To determine is there is a relationship between linoleic and linoleic content in gluteal fat tissue and serum lipids. Study site: five populations in Europe (Sweden, Netherlands, Belgium, Italy and Poland)	Three hundred and twenty-seven men aged 38 from five European towns. Specific details of general health, except for smoking habits were not presented in the paper. No dietary data was available for evaluation.	Fat biopsies taken from the upper outer quadrant of the left buttock. Serum lipids [total cholesterol, HDL-cholesterol and triglycerides] were determined enzymatically after an overnight fast. LDL-cholesterol determined by the Fridewald equation.	Adipse linoleic content, which varied widely was lowest in men from Poland (8.6%) and highest in men from Belgium (16.7%). Linoleic acid content was lowest in men from Italy (0.5%) and highest in men from Sweden and the Netherlands (0.9%). Linoleic acid was negatively correlated with LDL-C (-0.15, P< 0.01) and total cholesterol (r=-0.17, p<0.01). Linoleic acid was negatively correlated with serum triglycerides (r=-.14, p<0.05). There was a significant difference in HDL-C levels, with the highest level in men from Italy, Belgium, and Sweden and the lower concentration in men from Poland. Total cholesterol and LDL-C was highest in Italian males [TC=6.2 mmol/L and LDL-C= 4.2 mmol/L] but lowest in Swedish men [TC= 5.7 mmol/L and LDL-C= 3.9 mmol/L].	The authors concluded that there were major differences in these adipose unsaturated fatty acids from different European communities which correlated with some, but not all serum lipids. Adipsose linoleic and linolenic content did not adequately explain the significant differences observed in serum HDL-C and triglycerides.

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Study	Study Design	Subjects	Methods	Results	Comments
Brown, S. A., et al (Ref. 160)	Dietary intervention; dietician-instructed and multiple interviews; free-living; meals provided; food consumption supervised; dietary records maintained and checked. Purpose: measure effect of dietary cholesterol on blood lipids. Study site: Austria.	Study 1: 81 normolipidemic [less than 240 mg/dL fasting TC, 175 mg/dL LDL-C]; healthy outpatient males (aged 20 to 50 years, mean age 29.6 years). Study 2: 14 of the 81 males participated.	Study 1: Two diets (3 weeks each) of 6-week study. First 3 weeks: low chol diet (fat 40%; Carb 45%; protein 15% of total calories; Chol less than 300 mg/day). Second 3 weeks: similar to first 3 weeks plus 6 eggs per day (1,300 mg Chol/day). Diet fat consumption estimated based on percent of C-16 and C-18 for SFA, C-18:1 for MUFA and C:18:2 for PUFA. Study 1 fat content (% of calories total fat 38% SFA 11% MUFA 13% PUFA 6% Study 2. Four diets compared. 3 weeks/diet,k for a total 12 weeks. Percent of Carb and protein same as above. Estimate of fat distribution for study 2. Test diets 1 2 3 4 TF 45 44 45 44 SFA 11 11 8 8 MUFA 20 20 10 10 PUFA 7 7 20 20 chol (mg/d) 300 1,300 300 1,300	Study 1. In the 81 normotensive males, dietary cholesterol consumption increased total (12%), LDL-C (17%) and HDL-C (5%) significantly. Blood lipid data (mg/dL) 300 mg 1,300 mg TC 171 192 LDL-C 102 120 HDL-C 52 55 Study 2. LDL-C levels increased significantly (27%) on the high SFA-high cholesterol diet (diet 2) compared to SFA enriched diet with low cholesterol (diet 1). When subjects switched from SFA enriched, cholesterol rich diet to PUFA enriched low cholesterol diet; TC and LDL-C decreased significantly (31%) and HDL-C was unchanged (to diet 3). LDL-C was lowest on the PUFA enriched-low cholesterol diet. Adding cholesterol to PUFA increased LDL-C (25%) (diet 4). Study 2. Blood lipid (mg/dL) 1 2 3 4 TC 152 178 137 160 LDL-C 88 112 77 96 HDL-C 51 54 48 53	Results demonstrated that both dietary SFA and cholesterol increase total and LDL-C levels in normolipidemic males. The study included the use higher levels of total fat, dietary cholesterol and PUFA than is recommended for the general public.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Valsta, L. M. et al (Ref. 188)	Dietary intervention in free-living subjects. Cross-over design. Conventual mixed solid foods, meals provided and consumption monitored. Food records maintained. Duplicate portions of each diet collected daily and analyzed. Purpose: to compare effect of diets enriched in either MUFA of PUFA on serum lipoprotein Study site: Finland.	Fifty-nine healthy volunteers (30 men, 29 women), aged 18-65 years (median 25 years). At baseline subjects TC was 4.82 mmol/L or 186 mg/dL (men) and 5.23 mmol/L or 201 mg/dL (women). Subjects maintained normal lifestyle (same smoking habits, alcohol consumption, and exercise).	Study lasted 63 days. Baseline diet 2 weeks (SFA enriched), followed by two test diets (PUFA or MUFA enriched) for 25 days each. MUFA enriched diet used rapeseed oil and contained 5% SFA, 58% MUFA, 24% PUFA [n-6] and 13% PUFA [n-3]. PUFA enriched diet used sunflower oil and contained: 12% SFA, 23% MUFA, 65% PUFA [n-6]. Diets as % of total calories: BASE PUFA MUFA Fat 36 38 38 SFA 19 13 12 MUFA 11 10 16 PUFA 4 13 8 Chol (mg/d) 354 315 360	Dietary compliance assessed by plasma phospholipid fatty acids composition. Both PUFA and MUFA enriched diets significantly reduced TC and LDL-C from baseline. The MUFA enriched diet reduced TC and LDL-C more than PUFA enriched diet. Blood lipid data: mmol/L (mg/dL) BASE PUFA MUFA TC 5.3(205) 4.6(178) 4.5(174) LDL 3.2(123) 2.6(100) 2.4 (93) HDL 1.3 (51) 1.3 (50) 1.3 (51) The differences between test diets in TC and triglyceride (TG) were more pronounced in women but statically insignificant from men. Conversely, the test diets effected LDL-C and HDL-2 of men more than women.	MUFA enriched diets were shown to be equally effective as PUFA enriched diet in reducing TC and LDL-C levels in men and women. HDL-C was not significantly reduced by consumption of PUFA or MUFA enriched diet. If PUFA is at or below 10 to 13% calories, HDL-C levels do not appear to be lowered. Study results suggest cannot rely on Key equation to predict the effect of MUFA and PUFA on serum cholesterol levels.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Zock P. L. and Katan M. B. (Ref. 193)	Dietary intervention. Random, multiple cross-over design in healthy free-living subjects; uses three consecutive periods; three test diets lasting 3 weeks each. Meals provided. Duplicate portions of each diet were analyzed each day. Food diaries maintained. Purpose: To compare the effects of C-18 fatty acids on serum cholesterol levels: SFA (stearic acid); trans MUFA (elaidic acid); PUFA, (linoleate acid) Study site: Netherlands	Twenty-six men, 30 women normolipidemic, completed study. Equal number of men and women in each test group. Mean total cholesterol men and women was 157 mg/dL; HDL-C was 53 mg/dL. Age ranged 19 to 48 years for men, mean 25 years; Age ranged 18 to 49 years, mean 24 years for women.	Diets did not differ from one another other than test fatty acid which was 8% of total energy. Trans fatty acid (TFA) prepared from high oleic acid sunflower oil; hydrogenated with sulfurized nickel catalyst, and mixed 75 parts of TFA to 25 parts oleic acid rich oil. Stearate (S.A.) inter-esterified from a mixture of 41 parts of hydrogenated high linoleic acid sunflower oil to 50 parts high oleic sunflower oil and 9 parts of unmodified high linoleic sunflower oil. Diets as % of total calories: L.O. linoleate; Trans= trans elaidic; S.A.= stearate L.O. S.A. TRANS Fat 41 43 40 SFA 11 20 10 MUFA 16 17 23* PUFA 12 4 4 Chol (mg/MJ) 33 33 33 *7.7% as trans MUFA	Compared to levels of serum cholesterol on linoleate diet both stearate and trans fatty acid enriched diet significantly increased TC and LDL-C levels. In addition, both stearate and trans fatty acid enriched diet sifnificantly reduced HDL-C compared to linoleate enriched diet. Blood lipid data (mg/dL) L.O. S.A. TRANS TC 183 189 189 LDL 109 116 119 HDL 57 54 53	Consumption of trans fatty acid enriched diet which is closer to some subpopulation groups in U.S. increased blood risk factors for CHD. Broader spectrum of subjects than in earlier Mensink and Katan study. Trans fatty acid consumption of total calories and g/day: Current U.S. 3 to 4% or 7 to 10 g/day; Mensink and Katan study 11% or 33 g/day. The authors suggest that every one percent of energy from trans fatty acids increases LDL-C 1.2 mg/dL and lowers HDL-C 0.6 mg/dL relative to oleic and linoleic acid. Therefore at current U.S. consumption of 3 to 4% of calories, contributions from trans fatty acid could increase LDL-C by 4 mg/dL and decrease HDL-C by 2 mg/dL.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Mata P. et al (Ref. 175)	Dietary intervention in free-living healthy men and women. Controlled, cross-over design. Dietary diaries maintained. Compliance assessed by questionnare and observation. Consumed solid foods. Purpose: determine long- term effects of MUFA versus PUFA enriched diets on risk factors for CHD. Study site: Spain	Seventy-eight subjects from 2 urban closed communities (46 men mean age 33 years and 32 women mean age 42 years). Plasma cholesterol levels abouve 90th percentile and below 10th percentile were excluded from study (specific baseline data not provided in the study). Subjects maintained habitual lifestyle throughout study.	Maintained usual diets [men: fat 37% and Carb 43% of calories (2,540) and women: fat was 36% and carb 48% or 2,000 calories] with exception of type of dietary oil. Phase 1: subjects consumed PUFA enriched diet (sunflower oil-enriched in linoleic acid) for 12 weeks. Phase 2: subjects consumed MUFA enriched diet (olive oil-enriched in oleic acid) for 28 weeks. Vegetable oils comprised 44% of dietary fat (16% of total calories) for men and 50% or dietary fat (18% of calories for women). Diet composition as % of total calories PUFA MUFA FAT 37 36 SFA 12 12.5 MUFA 11 20 PUFA 12.8 3.4 CHOL 460 337 (mg/day)	Blood lipids were analyzed in week 10 and 12 of the PUFA enriched diet and weeks 4, 8, 12, 16, 28 weeks of the MUFA enriched diet. In this study the PUFA is the baseline of comparative diet. Phase I. Blood lipid data at 12 weeks (expressed in mmol/L and mg/dL Men Women TC 4.93(190) 5.2(201) LDL 3.3(126) 2.48(96) HDL 1.0(39) 1.3 (51) In phase 2 (at week 16 for men and 28 for women respectively, on the MUFA enriched diet): nonsignificant reduction in TC and LDL-C, but HDL-C increased significantly for men. In women: TC increased significantly (to 5.7 mmol/L (220 mg/dL or by 9%), LDL-C was unchanged (2.4 mmol?l or 94 mg/dL) and HDL-C increased significantly (to 1.7 mmol/L or 66 mg/dL or by 30%). No blood lipid data was provided for men at week 28 of study. The authors used an atherogenic index defined as (TC:HDL-C) to compare the effects of PUFA to MUFA diets: in men the atherogenic index fell 12% and 17% in women.	Larger and longer dietary intervention study than many of previous studies. The paper did not report baseline cholesterol values. Study which lasted up to 28 weeks allows for some estimation of possible long-term effects of MUFA compared to PUFA on blood lipids. Compared to the PUFA diet, the MUFA enriched diet significantly increased HDL-C levels without increasing TC or LDL-C for both men and women. The increase in HDL-C due to consumption of the MUFA enriched diet was larger in females than in males. Public health significance: diets were similar in the total fat content to the American diet, but had a higher percentage of MUFA suggest that longer term consumption may reduce total and LDL-C without reducing and perhaps increasing HDL-C levels.

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Study	Study Design	Subjects	Methods	Results	Comments
Garry P. J. et al (Ref. 167)	Longitudinal, nonrandom, free-living study design. Purpose: to estimate the effect of dietary intake from protein, fat carbohydrate, and total energy on plasma lipid levels in healthy, elderly men and women. Length of study 9 years. Study site: New Mexico and the United States	One hundred and fifty-seven healthy elderly men (n=65) and women (n=92) outpatients from Albuquerque, NM. All subjects > 60 years (medium age 70 were caucasians, who for the most part were health concsious and educated.	Dietician instructed, maintained food records. Nutrient content of diets analyzed. Analysis of blood was at the same time annually. Nutritional and clinical data collected from 1989 to 1989. Analyzed nutritional status also grouped by age (cross-sectional or cohort differences).	No significant cross-sectional differences in energy, protein total fat and carbohydrates intake with age was noted. There was a significant longitudinal decrease in total fat, saturated and PUFA and cholesterol intakes in men and women. Significant decreases in total, HDL-C and LDL-C plasma cholesterol concentrations were reported in both women and men. Blood lipid data mmol/L (mg/dL) Women Men TC 6.3(243) 5.6(217) LDL 4.1(158) 3.8(139) HDL 1.5(59) 1.3(52) Longitudinal predicted changes (mg/dL) Women Men TC -1.5 -2.2 LDL -0.9 -1.1 HDL -0.9 -1.1 The decrease in total fat and cholesterol intakes were significantly correlated with the decrease in total plasma cholesterol.	Study found significant associations between changes in dietary intake and changes in plasma lipids over time. When both SFA and PUFA intakes decreased over time, HDL-C was also reduced (therefore HDL-C reduced even when PUFA does not substitute for SFA).

TABLE—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Nguyen, L. B. et al (Ref. 194)	Dietary and drug intervention study. Controlled study in free- living subjects. Purpose: to determine the effects of cholesterol lowering drug and restriction of dietary cholesterol on synthesis and serum lipoprotein levels in two families with a lipid storage disease. Study site: New York and New Jersey	Two homozygous (male 28 years and female 9 years) and 2 obligate heterozygous subjects (female 25 years and male 47 years) with sitosterolemia, and 17 healthy control subjects (10 males and 7 females ranging between 19 and 60 years of age.	The metabolic ward diet consisted of: carbohydrate 53%, protein 17% and fat 30% of total calories, and cholesterol 223 mg/2,000 calories. Drug regiments consisted of: lovastatin (15 mg twice daily) and cholestyramine (15 g/day). The effect of diet alone on paired test subjects in a metabolic ward (one homozygous and one heteroxygous), diet in combination with drug regiments was conducted for 3 weeks each followed by a 2-week wash-out on the basal diet. A second pair of test subjects were on free-living dits (contained the similar caloric profiles but differed in sterol content [high= 400/500 g/day cholesterol and 100 to 150 mg/day plant sterols: low=100 g/cholesterol and 50 mg plant sterol/day). One free-living heterozygous subject received no drug treatment.	Both homozygous subjects had elevated cholesterol levels compared to controls [> 300 vs 185 mg/dl respectively]. Dietary sterol restriction was ineffective in lowering serum cholesterol levels in homozygous subjects. Neither lovastatin or low sterol diet produces a significant effect on reduced mononuclear leukocyte HMG-CoA reductase activity in homozygous or heterozygous subjects while lovastatin increased HMG CoA reductase 38% in controls.	Small study due to nature and rarity of the disease. Not all test subjects complied with both diet and drug treatments. Many confounders in study design and therefore difficult to make conclusions. There are marked conclusions. There are marked abnormalities in cholesterol homeostasis in patients with homozygous sisterolemia. The results suggested a depressed cellular cholesterol synthesis due to a deficiency in HMG-CoA reductase that cannot be up regulated by a low sterol diet. Can not make public health conclusions from this study.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Meinertz H. et al (Ref. 195)	A controlled dietary intervention study in free-living subjects. Purpose: to compare the effects of two sources of dietary protein (plant and animal) with dietary cholesterol on serum lipoproteins in healthy subjects. Study site: Denmark	Twenty-one healthy active individuals (11 women and 10 mean). Subjects had normal body weight, and normal cholesterol levels. Age range of subjects was 28 to 55 years.	All subjects received both the soy protein and the casein diets, with or without cholesterol enrichment in a cross-over design. Each dietary period lasted 31 days. The study included a 30-day wash-out period on a self selected diet. Diet composition (% total calories) Protein: Cas(g) Soy(g) (20%) 139 140 fat (27%) carbohydrate (53%) Cholesterol (mg) Low animal 72 12 plant 214 251 Cholesterol (mg) High animal 549 486 plant 579 637 casein = CAS soy protein = SOY Caloric intake from protein and fatty acid composition of both diets were very similar. SFA and stearic acids together was 11% of calories.	Body weight decreased on both diets casein and soy diets and on both low and high cholesterol diets. TC, triglycerides and VLDL-C levels were similar on casein and soy, regardless of the cholesterol content of the diets. On a low-cholesterol diets, the mean plasma levels of LDL-C and HDL-C were identical and not dependent on source of dietary protein. On a cholesterol enriched diet, however, LDL-C levels were significantly lower on the soy protein diet and HDL-C was significantly higher. Blood lipid data (mg/dL) Low Chol / Enriched Chol CAS SOY CAS SOY TC 124 127 138 133 LDL 68 66 81 68 HDL 42 43 47 53	Results suggest an interaction between source of dietary protein (plant and/or animal) and dietary cholesterol on levels of blood LDL-C and HDL-C concentrations. On cholesterol enriched diet, the source of dietary protein appears to be more important in determining serum cholesterol levels than on a low cholesterol diet. This study is of public health significance, since the results suggest that on a cholesterol enriched diet, such as found in the U.S., casein (animal protein) increased LDL-cholesterol while simultaneously reducing the HDL- cholesterol.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Barr S. L. et al (Ref. 220)	Dietary intervention study. Randomized, double blind and controlled study in free-living subjects. Purpose: to compare the effects of a low fat diet and a low fat diet that is reduced in saturated fat on blood cholesterol levels in healthy males. Study site: New York	Forty-eight healthy males ages 21 to 32 years. Subjects with extreme dietary habits or ethanol intake were excluded. Other: men BMI 24 Baseline lipids (mg/dL): ADD Step 1 Sat TC 185 185 179 HDL 46 49 49 LDL 139 135 130 n=17 n=15 n=16	All subjects consumed baseline diet (3 weeks) equivalent to average American diet (AAD). Meals provided throughout 10-week study. Randomly assigned to three isocaloric diet groups (7 weeks). Group 1 (ADD); group 2 (AHA Step 1); group 3 (AHA + SFA). Diet composition % of total calories AAD Step 1 SAT Fat 36 29 29 SFA 14 8.6 12 MUFA 14 12.6 10.6 PUFA 7 7.6 6.3 Chol (mg/d) 491 303 347	Refer to baseline data: Overall the switch to Step 1 diet significantly decreased total cholesterol by 0.36 mmol/L or 14 mg/dL (7.5%). Men on SFA/Step 1 diet had non-significant decrease in total cholesterol of 0.08 mmol/L or 3.1 mg/dL (1.6%) compared to AAD diet. Switch to Step 1 diet significantly decreased LDL-cholesterol 0.25 mmol/L or 9.6 mg/dL (8.1%). Consumption of SFA diet was associated with a decrease of 0.03 mmol/L or 1.1 mg/dL (1.1%). Switch to Step 1 diet significantly decreased HDL-cholesterol 0.11 mmol/L or 4.2 mg/dL (8.6%). Switch to SFA diet decreased HDL-cholesterol by 0.06 mmol/L or 2.3 mg/dL (4.6%.)	No significant decreases in total or LDL-cholesterol were observed in healthy males when total calories from fat was reduced from 37% to 30%. Significant reductions in total and LDL-cholesterol were observed in healthy males when both total fat and saturated fat content of the diet was reduced.
Lehtimaki, T. et al (Ref. 221)	Dietary intervention study. Controlled, switch-back in free-living subjects. Purpose: to compare the effect of dietary cholesterol on blood lipids and apolipoprotein E phenotype in healthy males and females. Study site: Finland	Thirty-six normolipidemic students (16 female and 20 males, average age 23.9 years). Apo phenotype were: E3/2 (n=9); E3/3 (n=11); E4/4 (n=3). Baseline lipids for all subjects estimated from figure of data at zero time: TC range (4.5 to 5.2 mmol/L (174 to 201 mg/dL)); LDL-C (2.4 to 2.9 mmol/L (93 to 112 mg/dL)) and HDL-C (1.4 to 1.7 mmol/L (54 to 66 mg/dL)]) Other: All participants were nonsmokers, used minimal alcohol, mean 21.9 BMI.	Baseline diet (3 weeks), followed by 3 week diet intervention which was followed by 3 week return to baseline diet. No eggs consumed on baseline diets. Dietary intervention included addition of three eggs (yolks)/day or addition of 750 mg extra dietary cholesterol. Energy intake was not measured during intervention. Body weights unchanged during the study.	There were no significant differences between males and females either during intervention or switchback. Three week of cholesterol enriched diet induced significant increase in total and LDL-cholesterol, and apo B concentration in all 4 phenotypes. In all phenotype groups, HDL-cholesterol increased with dietary cholesterol consumption. All lipid classes returned to original concentrations after switchback. The response in blood LDL-cholesterol and apo B to the cholesterol rich diet was greater in apo E4/4 subjects. The above statements on response to dietary cholesterol are the authors and supported by figures of the data in the paper.	Insufficient dietary data provided to evaluate study accurately. Did not record saturated fat and cholesterol contents in the baseline and intervention diets. Stronger responses by apo E4/4 phenotypes, suggests these individuals are more sensitive to dietary cholesterol (increased two-fold over other phenotypes). In Finland about 6% of the population is of the apo E4/4 phenotype.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Tremblay, A. et al (Ref. 217)	Diet and exercise intervention study in free-living subject. Individual recorded dietary records for 1 day /week throughout study. Meet once per week with dietitian and exercise specialist. Purpose: to determine the effect of a low fat diet and exercise on metabolic profiles (including blood lipids) in obese woman. Study site: Canada	Four obese women, average age 42 years. On an average body weight was 92 kg, and % body fat 49. Baseline blood lipids (mg/dL): TC 214 LDL 157 HDL 38 TG 126	29-month study which included two experimental periods [period one (15 months) involved supervised aerobic exercise and the second period involved exercise plus low fat diet]. The dietary intervention by instruction was to maintain protein (0.9 g/kg body weigh) and carbohydrate intake but to reduce lipid consumption to 26 to 28% of total calories (no indication of what baseline macronutrient intake was).	Lipid intake in period 1 and 2 was 29 and 30% of total calories. A significant decrease in body weight, fat mass and percent body fat occurred in period 1. Substantial reductions in plasma cholesterol [from 214 down to 174 mg/dL] and LDL-cholesterol [157 down to 116 mg/dL] were observed in period 1 and 2. Plasma HDL-cholesterol was not changed [38 compared to 40 mg/dL] but apo A-1 (HDL) was significantly increased by exercise [105 compared to 122 mg/dL].	At end of 29 months subjects lost 11 kg (but were still obese). Plasma glucose and insulin response to oral glucose similar to nonobese subjects. Interventions appeared to normalize level or risk for diabetes which is also a risk factor for CHD. Results (n=4) suggested that long-term exercise program can reduce plasma total and LDL-cholesterol levels in obese subjects.
Bonanome, A. et al (Ref. 219)	A randomized, cross-over design, dietary intervention study in free-living subjects. Purpose: To compare the effects of MUFA and PUFA on blood lipids and the susceptibility of LDL-cholesterol to oxidation. Study site: Pauda Italy.	Eleven healthy males, mean age 22 years, body weight 76 kg and body mass index of 25. Blood lipid profile of subjects: blood cholesterol (4.68 mmol/L or 181 mg/dL); LDL-cholesterol of 3.2 mmol/L or 125 mg/dL and HDL-cholesterol of 1.1 mmol/L or 44 mg/dL.	Two solid food diets with each diet lasting 3 weeks separated by washout period of 7 days. Phase 1 was enriched in MUFA and phase 2 was enriched in PUFA. Dietary composition (% of total calories) MUFA PUFA Fat(45%) SFA 10 10 MUFA 30 5 PUFA 5 30 chol <200 <200 Grapeseed oil supplied most of PUFA in diet. Olive oil supplied most of MUFA in diet. Other: susceptibility to oxidative modification was measure in 2, 2'azobis (2-aminopropane) dihydro-choloride (AAPH). AAPH is a water-soluble diazo compound that generates free radicals by spontaneous thermal decomposition.	Both diets significantly lowered total and LDL-cholesterol. Blood lipid data mmol/L (mg/dL) Baseline MUFA PUFA TC 4.7(181) 3.8(148) 3.5(134) LDL 3.2(125) 2.6(100) 2.3 (90) HDL 1.1(44) 1.0 (40) 0.98(38) TG 1.1 0.8 0.7 Other: The peroxidation rate was significantly higher when patients were on PUFA diet compared to MUFA diet. No significant differences were observed for inhibition of peroxidation by either diet.	Replacement of calories from SFA by either MUFA or PUFA induced a significant hypocholesterolemic effect. In addition, the results of the study support the hypothesis that diets rich in MUFA increase resistance of LDL-cholesterol to oxidative modification, independent of their content of antioxidants. Changes in peroxidation rate suggest that once LDL-cholesterol is depleted of antioxidant content, a diet enriched in MUFA may allow LDL-cholesterol to resist oxidative stress. Ration of oleic to linoleic in LDL was inversely correlated with the peroxidation rate.

TABLE--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Zimetbaum, P. et al (Ref. 218)	Epidemiological, prospective study. Purpose: to access the correlation of lipid and lipoproteins levels on CVD risk, stroke, dementia, and death in the elderly. Study site: New York, (10-year follow-up of the Bronx Aging Study (BAS))	Mean age of entry into BAS study was 79 years, who did not have any diagnosed terminal illness or dementia. From BAS enrollment of 488, 350 had two lipid determinations at 10 years. Subjects had about a 7 to 9 th grade education, 60% were men and 25% of women were smokers, 48% of subjects took diuretics.	Extensive medical and psychological histories taken, laboratory screening, neurological and neuropsychiatric testing. CVD included MI, stroke and other heart related deaths. All events verified by reviewing medical records and/or death certificates.	Mean blood lipid values: (mg/dL) Total Men Women chol 201 234 LDL-C 140 158 HDL-C 38 46 Proportional hazards analysis showed that men with consistently low HDL-cholesterol levels (<30 mg/dL) were independently associated with the development of MI, CVD and/or death. For women, elevated LDL-cholesterol (>171 mg/dL) was associated with MI.	Using both univariant and multivariant analysis, only a consistently low HDL-cholesterol was significantly and independently associated with MI or all cause mortality in elderly men even after controlling for smoking and hypertension. For elderly women only a consistently elevated LDL-cholesterol was associated with MI. No significant associations between lipids and dementia were observed for either men or women. These results are in contrast to Framingham report which reported that baseline low HDL-cholesterol levels was associated with increased risk of MI and or death in both elderly and middle aged men and women. Elevated total cholesterol was not found to be an independent risk factor for MI or death.

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