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RE: Qualified Health Claim Petition – Unsaturated Fatty Acids from Canola Oil and
Reduced Risk of Coronary Heart Disease (Docket No. 2006Q-0091)

Dear Dr. Johnson:

This letter responds to the health claim petition dated January 7, 2006, submitted to the Food and Drug Administration (FDA or the agency) by the U.S. Canola Association pursuant to Section 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(4)). You are listed in the petition as the person to whom correspondence should be addressed. The petition requested that the agency authorize a qualified health claim characterizing the relationship between the consumption of unsaturated fatty acids (UFAs) from canola oil and a reduction in risk of coronary heart disease (CHD). This petition proposed as a model qualified health claim:

“Canola oil (19 grams – about 1 ½ tablespoons per day) may reduce the risk of coronary heart disease due to its unsaturated fat content, according to supportive but not conclusive research. Canola oil should replace a similar amount of saturated fat in the diet without increasing calories.”

FDA filed the petition on March 2, 2006 as a qualified health claim petition and posted the petition on the FDA website for a 60-day comment period, consistent with the agency's guidance on procedures for qualified health claims.¹

The agency received one comment on this petition. The comment supported the claim unconditionally. FDA considered the comment in its evaluation of this petition.

This letter sets forth the basis of FDA's determination that the current evidence for the proposed health claim is appropriate for consideration of a qualified health claim on conventional foods. This letter also sets out the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim with respect to consumption of UFAs from canola oil and a reduced risk of CHD.

¹ See guidance entitled "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements," July 10, 2003. [<http://www.cfsan.fda.gov/~dms/nuttf-e.html>]

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I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.² In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.³ FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.⁴

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.⁵

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,⁶ review articles,⁷ and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in meta-analyses and review articles prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications⁸ to identify reports of additional studies that

² See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

³ See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003. [<http://www.cfsan.fda.gov/~dms/hclmgu4.html>]

⁴ For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.

⁵ In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See guidance entitled "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements," December 22, 1999. [<http://www.cfsan.fda.gov/~dms/ssaguide.html>]

⁶ A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

⁷ Review articles summarize the findings of individual studies.

⁸ Other examples include book chapters, abstracts, letters to the editor, and committee reports.

may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (IOM, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or a statistical analysis means that scientific conclusions cannot be drawn from the study (Spilker et al., 1991; Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then ranks the strength of the total body of publicly available evidence.⁹ The agency conducts this ranking process by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated¹⁰, and the overall consistency¹¹ of the total body of evidence.¹² Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified UFAs from canola oil as the substance that is the subject of the proposed claim. UFAs are fat components that occur naturally in many foods. Therefore, the agency concludes that UFAs from canola oil, identified in the petition, are a component of food and thus meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

Canola oil, also known as low erucic acid rapeseed (LEAR) oil, is the fully refined, bleached, and deodorized edible oil obtained from certain varieties of *Brassica Napus* or *B. Campestris* of the family *Cruciferae*. The plant varieties are those producing oil-bearing seeds with a low erucic acid content (21 CFR 184.1555(c)(1)).

FDA has not been petitioned to authorize a health claim or exercise its enforcement discretion for a qualified health claim for any vegetable oil high in UFAs, except for canola oil (LEAR oil). However, vegetable oil manufacturers and others may petition the agency to allow for the use of claims for vegetable oils high in UFAs relative to saturated fatty acids (SFAs). Health claim petitions must include all of the information required in 21 CFR 101.70, including scientific evidence that supports the relationship between a substance and a disease or health-related condition.

⁹ See *supra*, note 3.

¹⁰ Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990).

¹¹ Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B. The environment and disease: association or causation? *Proc R Soc Med*, 58:295-300, 1965.); See also Evidence Report/Technology Assessment No. 47, *Systems to Rate the Strength of Scientific Evidence*, Agency for Healthcare Research and Quality, defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."

[<http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents>]

¹² See *supra*, note 3.

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified CHD as the disease that is the subject of the proposed qualified health claim. The agency concludes that CHD is a disease and therefore the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify the claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is GRAS, approved as a food additive, or authorized by a prior sanction issued by FDA (see 21 CFR 101.70(f)).

The petition asserts that UFAs are ubiquitous, natural components of the food supply that are safe and lawful. The petition also asserts, under 21 CFR 101.14(b)(3)(i), that UFAs provide nutritive value to the diet by serving as a source of energy and, furthermore, certain individual UFAs contribute technical effects. Examples of UFAs with technical effects are oleic acid, which has been authorized as a direct food additive for use as a lubricant, binder, and a defoaming agent (21 CFR 172.860), and linoleic acid, which has been authorized for use in foods as a flavoring agent, adjuvant, and nutrient supplement (21 CFR 184.1065). FDA agrees that UFAs are ubiquitous, natural components of the food supply that provide nutritive value to the diet and that certain individual UFAs contribute technical effects.

In order to receive a possible benefit from consumption of UFAs from canola oil and a reduced risk of CHD, the scientific evidence suggests that the daily minimum amount of UFAs from canola oil that should be consumed in place of foods high in SFAs, while not increasing caloric intake, is approximately 17.7 g of UFAs, which corresponds to about 19 g of canola oil (see Section IV, paragraph F). An intake of 19 g of canola oil provides approximately 171 calories but because the qualified health claim specifies that canola oil is to replace saturated fat in the diet while not increasing caloric intake, an individual's total fat intake should not increase based on the recommendations in the claim.

UFAs can be separated into two categories: monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). Based on a lack of information on adverse effects, a Tolerable Upper Intake Level (UL) for MUFAs has not been set by the Institute of Medicine (IOM) and because of insufficient evidence relating low and high intakes of MUFAs and chronic disease, an Acceptable Macronutrient Distribution Range (AMDR) was not provided by the IOM. Median MUFA intake, however, ranges from approximately 25 to 39 g/day for men and

18 to 24 g/day for women (IOM, 2002). According to data from USDA (U.S. Department of Agriculture, 2005), 19 g of canola oil would provide 11.2 g of MUFAs.

The IOM has classified PUFAs into two categories: n-3 PUFAs and n-6 PUFAs. According to data from the USDA (U.S. Department of Agriculture, 2005), the PUFAs in canola oil consist solely of n-6 PUFAs. Based on a lack of information on adverse effects, a UL has not been set for n-6 PUFAs. Lacking safety data upon which to base a UL, the IOM has established an AMDR of five to ten percent of energy for n-6 PUFAs. The ten percent of energy "upper boundary" for the AMDR is based on the approximate highest intake levels for individuals in North America (IOM, 2002). The Continuing Survey of Food Intakes by Individuals, 1994-1996, 1998, which represents a wide range in the amount of foods consumed in the U.S., showed that the 99th percentile of n-6 PUFAs intake for all individuals (31.3 g/day) would exceed the sum of the median intake of PUFAs (12 g/day) plus the PUFAs from 19 g of canola oil (5.6 g/day). Because the 99th percentile of intake was used to set the upper boundary of the AMDR for n-6 PUFAs, consuming 19 g of canola oil per day falls well within the boundaries of the AMDR for n-6 PUFA intake.

UFAs are ubiquitous, natural components of the food supply that provide nutritive value to the diet, certain individual UFA components have been approved as direct food additives or authorized for use in foods, and the level of UFAs from canola oil necessary to justify the claim should not increase an individual's total fat intake due to the replacement of SFAs in the diet. Therefore, FDA concludes that under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), the use of UFAs from canola oil at levels necessary to justify the claim is safe and lawful.

II. The Agency's Consideration of a Qualified Health Claim

FDA has identified the following disease endpoints to use in identifying CHD risk reduction for purposes of a health claim evaluation: the incidence of coronary events (myocardial infarction (MI), ischemia), cardiovascular death, coronary artery disease, atherosclerosis. The following surrogate endpoints for identifying CHD risk reduction for purposes of a health claim evaluation were used high blood pressure, blood (serum or plasma) total cholesterol, and blood (serum or plasma) low density lipoprotein (LDL)-cholesterol levels.¹³ These disease and surrogate endpoints were used to evaluate the potential effects of UFAs from canola oil on CHD risk. The petition cited 113 publications as evidence to substantiate the relationship for this claim. These publications consisted of: 18 review articles; one animal study; seven publications from National Institutes of Health (NIH), American Heart Association and various trade associations; one letter to the editor; 37 studies that did not evaluate the substance and disease relationship; seven meta-analyses and 42 articles that evaluated the substance and disease relationship.

A. Assessment of Background Materials

¹³ National Heart, Blood and Lung Institute (NHLBI), Heart and Blood Vessel Diseases (http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html) and National Cholesterol Education Program, Page 3 (U.S. Department of Health and Human Services, 2001, http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm).

"Background materials" here refers to review articles, meta-analyses, letters to the editor, and federal and non-profit association reports. Although useful for background information, these materials do not contain sufficient information on the individual studies that they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information on studies summarized in these materials prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the background materials supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

B. Assessment of Animal Studies

FDA also uses animal studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal study submitted with the petition as supportive information about the substance - disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of any type of food allergy, nor can the studies mimic the human body's response to the consumption of UFAs from canola oil. Therefore, FDA cannot draw any scientific conclusions from the animal study regarding UFAs from canola oil and CHD risk reduction.

C. Assessment of the Intervention Studies

FDA identified 42 intervention studies for its evaluation of the relationship between consumption of UFAs from canola oil and risk of CHD. Scientific conclusions could not be drawn from 34 of the 42 studies regarding the substance/disease relationship for one or more of the following reasons.

- Five studies did not measure a validated surrogate endpoint of CHD (i.e., blood total-cholesterol, blood LDL-cholesterol, blood pressure) (See Appendix 1). Because these studies did not measure a validated surrogate endpoint, scientific conclusions about the relationship between consumption of UFAs from canola oil and risk of CHD could not be drawn.
- Eighteen studies did not include a control group consuming SFAs for comparison to the relative effects of UFAs from canola oil (see Appendix 1). Therefore, it could not be determined if the replacement of SFAs with UFAs from canola oil reduced the risk of CHD. Hence, scientific conclusions could not be drawn from these studies.

- The duration of the study intervention was too short (less than three weeks) in nine studies (see Appendix 1) to adequately determine if changes in serum cholesterol levels were reflective of the intervention treatment (Bonanome et al., 1988). Hence, scientific conclusions could not be drawn from these studies.
- Five studies used UFAs that were not solely from canola oil and thus FDA could not determine if the effects were from UFAs from canola oil or from other types of oil (See Appendix 1). Therefore, no scientific conclusions could be drawn from these studies.
- Three studies (see Appendix 1) were a republication of another study and therefore these studies provided no new scientific evidence to support the substance and disease relationship.

Eight of the 42 intervention studies evaluated the relationship between UFAs from canola oil and CHD risk by replacing SFAs with UFAs from canola oil (Baudet et al., 1988; Lichtenstein et al., 1993; Sundram et al., 1995; Wardlaw et al., 1991; Sarkkinen et al., 1998; Uusitupa et al., 1994; Matheson et al., 1996; Noakes et al., 1998). Four of these studies provided all of the meals and snacks to the subjects and thoroughly controlled for all aspects of the dietary intervention (Baudet et al., 1988; Lichtenstein et al., 1993; Sundram et al., 1995; Wardlaw et al., 1991). In contrast, four studies relied on the participants to prepare and consume the diets at home, based on study instructions (Sarkkinen et al., 1998; Uusitupa et al., 1994; Matheson et al., 1996; Noakes et al., 1998). Both types of studies are considered to be an intervention design. However, the four studies that strictly controlled the subject's dietary intakes provide stronger evidence for the substance/ disease relationship since compliance was strictly monitored. Sundram et al. (1995) received a high methodological quality rating and the remaining seven studies received moderate methodological quality ratings. The eight studies are summarized below.

Baudet et al. (1988) was a randomized cross-over study in 20 nuns from France. The study compared a diet high in SFAs from butter and cream to a diet containing UFAs from low erucic acid rapeseed oil. The diets were six weeks in duration and all meals were provided to the subjects. The LEAR diet significantly ($p < 0.05$) reduced serum total- and LDL-cholesterol levels compared to the saturated fat-containing diet.

Lichtenstein et al. (1993) conducted a randomized, crossover intervention study in 14 subjects (six males and eight females) from the United States. The study compared a diet high in SFAs to a diet high in UFAs from canola oil. The subjects were on each diet for 32 days and all of the meals and snacks were provided. The consumption of UFAs from canola oil significantly ($p < 0.05$) reduced serum total- and LDL-cholesterol levels compared to the diet containing high levels of SFAs.

Thirty two males from the United States were placed on a diet high in saturated fat for three weeks and then were randomized to either a diet containing UFAs from canola or safflower oils for eight weeks (Wardlaw et al., 1991). The study provided all of the meals and snacks for the

subjects. The diet rich in UFAs from canola oil significantly ($p < 0.01$) reduced serum total- and LDL-cholesterol levels compared to the diet high in SFAs.

Uusitupa et al. (1994) conducted a randomized crossover study in ten females from Finland. The women consumed either a diet high in SFAs or a diet high in UFAs from canola oil for three weeks. The subjects were given written instructions about the diets and prepared their own meals. The subjects kept seven-day food records to aid in monitoring compliance. Both serum total- and LDL-cholesterol levels significantly decreased ($p < 0.05$) when the subjects consumed the UFA canola oil diet compared to the SFA diet.

A randomized crossover study in 38 mildly hypercholesteremic subjects (21 males; 17 females) from Australia compared a diet high in SFAs and one high in UFAs from canola oil (Noakes et al., 1995). The subjects were provided with test spreads and biscuits made with the respective fat source, but prepared most meals on their own. The subjects kept detailed food records for three days during each three week intervention period. The diet containing UFAs from canola oil significantly reduced ($p < 0.05$) serum total- and LDL-cholesterol levels compared to the diet containing SFAs.

Matheson et al. (1996) conducted a crossover intervention study in 23 subjects (22 males and one female) participating in a research expedition in the Australian Antarctic substation. The study consisted of three dietary interventions; a diet providing SFAs for 16 weeks, a diet containing UFAs from canola oil for 13 weeks, and then a diet providing SFAs for 13 weeks. The subjects were provided special spreads and oils to adjust the fatty acid content of their diet, however, the subjects self selected the rest of their diets based on the food served at the substation. Food records were collected to evaluate the dietary intake of the subjects during every intervention period. The diet containing UFAs from canola oil lowered serum total- and LDL-cholesterol levels compared to the first SFA diet ($p < 0.05$), but not the second SFA dietary intervention.

Sundram et al. (1995) conducted a double-blind crossover study in Malaysia with 23 male subjects. The subjects first consumed a diet high in saturated fat for four weeks and then consumed a diet high in UFAs from canola oil. All meals and snacks were provided to the subjects for the entire duration of the study. There were not any differences in serum total- or LDL-cholesterol levels between the two different diet periods.

Sarkkinen et al. (1998) conducted a randomized, single-blinded intervention trial in 77 (36 males and 41 females) mild to moderate hypercholesteremic Finnish subjects. The subjects were randomized to either a diet containing high levels of SFAs or a diet containing UFAs from canola oil for six months. The subjects were instructed on their dietary intervention and provided with different oils and fat spreads. Adherence to the intervention was monitored using food records. Consuming UFAs from canola oil did not affect serum total- and LDL-cholesterol levels compared to subjects consuming diets high in SFAs.

D. Assessment of the Observational Studies

There were no observational studies available to the agency that evaluated the relationship between the replacement of diets containing high levels of SFAs with UFAs from canola oil and risk of CHD.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of various types of studies and sample sizes), whether the body of evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,¹⁴ and the overall consistency¹⁵ of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

Based on the discussion in Section II above, the totality of the scientific evidence in this case includes eight intervention studies (Baudet et al., 1988; Lichtenstein et al., 1993; Sundram et al., 1995; Wardlaw et al., 1991; Sarkkinen et al., 1998; Uusitupa et al., 1994; Matheson et al., 1996; Noakes et al., 1998). Four of the intervention studies strictly controlled the dietary intervention of subjects (Baudet et al., 1988, Lichtenstein et al., 1993, Sundram et al., 1995, Wardlaw et al., 1991) and three of these studies reported that UFAs from canola oil reduced serum total- and LDL-cholesterol levels compared to diets containing high levels of SFAs (Baudet et al., 1988, Lichtenstein et al., 1993; Wardlaw et al., 1991). The fourth strictly controlled study by Sundram et al. (1995) found no effect of UFAs from canola oil on serum total- and LDL-cholesterol levels compared to diets containing high levels of SFAs. The four intervention studies that allowed the subjects to prepare their own meals reported similar results to the strictly controlled trials in that three studies reported a beneficial relationship (Uusitupa et al., 1994; Matheson et al., 1996; Noakes et al., 1998) while one found no relationship (Sarkkinen et al., 1998) between a diet containing UFAs from canola oil and a diets containing high levels of SFAs.

Based on FDA's review of the strength of the total body of scientific evidence for the proposed claim, FDA concludes that the scientific evidence is credible and supports the substance/disease relationship. However, due to the small number of subjects in the six intervention studies that showed a beneficial relationship and the fact that three of these six studies did not strictly control the diets, FDA believes that the scientific evidence represents a low level of comfort among qualified scientists that the claimed relationship is scientifically valid. Therefore, FDA intends to consider the exercise of its enforcement discretion for a qualified health claim about UFAs

¹⁴ See *supra*, note 10.

¹⁵ See *supra*, note 11.

from canola oil on the label or in labeling of canola oil that includes a truthful and non-misleading description of the strength of the body of scientific evidence, e.g., "limited and not conclusive scientific evidence suggests."

IV. Other Enforcement Discretion Factors

Factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims about UFAs from canola oil and reduced risk of CHD are discussed below.

For the purpose of this enforcement discretion letter, the following definitions will be used: (1) "canola oil" means products that are essentially pure canola oil and are labeled as such¹⁶; (2) "vegetable oil spread" means margarine (21 CFR 166.110) and margarine-like products, formulated to contain canola oil; (3) "dressings for salads" means dressings for salads formulated to contain canola oil; (4) "shortenings" means vegetable oil shortenings, formulated to contain canola oil; and (5) "canola oil-containing foods" means all other foods, such as sauces or baked goods, formulated to contain canola oil, excluding canola oil, canola oil spreads, dressings for salads, and shortenings. The term "canola oil products" refers to items numbered 2 - 5 in the above list.

A. Total fat, Saturated Fat, and Cholesterol Criteria for CHD-related Health Claims

In regulations authorizing CHD-related health claims, FDA has generally required, with a few exceptions, that foods bearing the claims meet the "low fat" criterion defined by 21 CFR 101.62(b)(2), "low saturated fat" criterion defined by 21 CFR 101.62(c)(2), and the "low cholesterol" criterion defined by 21 CFR 101.62(d)(2) (see authorized claims in 21 CFR §§ 101.75, 101.77, 101.81, 101.82, and 101.83). The agency will discuss below how it intends to consider these criteria as factors in deciding whether to exercise its enforcement discretion for a qualified health claim for UFAs from canola oil and CHD risk on canola oil, vegetable oil spreads, dressings for salads, shortenings, and canola oil-containing foods. Later in Section B, FDA discusses total fat, saturated fat, and cholesterol content relative to the general requirements for health claims (21 CFR 101.14), specifically, disqualifying levels (21 CFR 101.14(a)(4)).

"Low fat" criterion

FDA has required in the past that foods bearing CHD-related health claims meet the requirement for "low fat" as defined by 21 CFR 101.62(b)(2) as foods that contain less than 3 g of fat per reference amount customarily consumed (RACC), or, for foods with a RACC of less than 30 g or less than 2 tablespoons, per 50 g. The requirement of the "low fat" criterion was first introduced in the dietary lipid and cardiovascular disease proposed rule (56 FR 60727 at 60739; November 27, 1991). FDA stated that, while total fat is not directly related to increased risk for CHD, it may have significant indirect effects. The agency stated that low fat diets facilitate reduction in the intake of saturated fat and cholesterol to recommended levels. Furthermore, the agency

¹⁶ FDA intends to exercise its enforcement discretion for canola oil and certain products containing canola oil, as such products were included in the studies that suggested benefit.

noted that obesity is a major risk factor for CHD, and dietary fats, which have more than twice as many calories per gram as proteins and carbohydrates, are major contributors to total calorie intakes. There have been several exceptions to this criterion in the past. Products derived from whole soybeans without added fat are exempted from the "low fat" criterion in the soy protein and CHD health claim (21 CFR 101.82(c)(2)(iii)(C)). In the plant sterol/stanol esters and CHD health claim, FDA does not require foods bearing the claim to meet the "low fat" criterion but requires that total fat level of foods not exceed the total fat disqualifying level (21 CFR 101.14(a)(4)) with an exception for spreads and dressings for salads on a per 50 g basis (21 CFR 101.83(c)(2)(iii)(C)). In not requiring the "low fat" criterion, FDA noted that the Dietary Guidelines for Americans, 2000 (HHS and USDA, 2000) recommended choosing a diet that is low in saturated fat and cholesterol and moderate in total fat. Specifically, the Dietary Guidelines for Americans, 2000 recommended moderate amounts of foods high in unsaturated fat with a caution to avoid excess calories. More recently, FDA has exempted from the "low fat" criterion olive oil, vegetable oil spreads, dressings for salads, shortenings, and olive oil-containing foods that bear a MUFAs from olive oil and CHD qualified health claim (<http://www.cfsan.fda.gov/~dms/qhcolive.html>). In the Dietary Guidelines for Americans, 2005, the recommendation for total fat intake was modified to an intake between 20 to 35 percent of calories, with most fats coming from sources of PUFAs and MUFAs (HHS and USDA, 2005).

Canola oil exceeds the "low fat" criterion because it is essentially entirely fat. Furthermore, FDA intends to exercise enforcement discretion for canola oil products that contain 4.75 g or more canola oil per RACC (see Section F), and thus would not meet the "low fat" criterion. The most and less persuasive scientific studies that suggest a relationship between UFAs from canola oil in replacement of SFAs and reduced risk of CHD used canola oil in cooking, as well as several types of foods containing canola oil. The UFAs from canola oil and CHD qualified health claim will inform consumers that they may lower their risk of CHD by consuming UFAs from canola oil and canola oil products in place of SFAs, while not increasing caloric intake. FDA believes this type of dietary information will help consumers maintain healthy dietary practices by providing consumers with information that can facilitate reductions of saturated fat and cholesterol intake since canola oil contains no cholesterol and less saturated fat than other fat sources. Canola oil is a plant food and does not contain cholesterol. Furthermore, FDA concurs with current dietary guidelines that consuming diets low in saturated fat and cholesterol is more important in reducing CHD risk than consuming diets low in total fat. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that canola oil, vegetable oil spreads, dressings for salads, shortenings, and canola oil-containing foods that bear a UFAs from canola oil and CHD qualified health claim meet the "low fat" criterion.

"Low saturated fat" criterion

"Low saturated fat," as defined by 21 CFR 101.62(c)(2), means that the food must contain less than 1 g of saturated fat per RACC and not more than 15% of calories from saturated fat. A RACC of canola oil contains approximately 0.994 g of saturated fat and 7.1% of calories from saturated fat. Canola oil meets the definition of a "low saturated fat" food.

A low saturated fat nutrient content requirement would not limit the use of a qualified health claim for UFAs from canola oil and CHD risk to be used on the label or in labeling of canola oil. Several vegetable oil spreads, dressings for salads, shortenings, and canola oil-containing foods may contain saturated fat from sources other than canola oil. Saturated fat is known to increase blood total- and LDL-cholesterol levels, which is a risk factor for CHD. Therefore, FDA intends to consider, in its exercise of enforcement discretion, that canola oil, vegetable oil spreads, dressings for salads, shortenings, and canola oil-containing foods labeled with a UFAs from canola oil and CHD qualified health claim meet the "low saturated fat" criteria as defined in 21 CFR 101.62(c)(2).

"Low cholesterol" criterion

Like all plant-based foods, canola oil does not contain cholesterol, and therefore, a low cholesterol nutrient content requirement would not limit the use of a qualified health claim for UFAs from canola oil and CHD risk to be used on the label or in labeling of canola oil. Several vegetable oil spreads, dressings for salads, shortenings and canola oil-containing foods may contain cholesterol from sources other than canola oil. Dietary cholesterol is known to increase blood total- and LDL-cholesterol levels, which is a risk factor for CHD. Therefore, FDA intends to consider, in its exercise of enforcement discretion, that canola oil, vegetable oil spreads, dressings for salads, shortenings, and canola oil-containing foods labeled with a UFAs from canola oil and CHD qualified health claim meet the "low cholesterol" criteria as defined in 21 CFR 101.62(d)(2).

B. Disqualifying Nutrient Levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)), a food may not bear a health claim if that food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in § 101.14(a)(4). Disqualifying total fat levels for individual foods are above 13.0 g per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying saturated fat levels for individual foods are above 4.0 g per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying cholesterol levels for individual foods are above 60 mg per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying sodium levels for individual foods are above 480 mg per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g.

The general requirements for health claims also provide for FDA to authorize a health claim for a food despite the fact that a nutrient in the food exceeds the disqualifying level, if the agency finds that such a claim will assist consumers in maintaining healthy dietary practices (21 CFR 101.14(e)(3)). In such cases, the label must also bear a disclosure statement that complies with 21 CFR 101.13(h), highlighting the nutrient that exceeds the disqualifying level.

The application of these regulatory provisions to UFAs from canola oil and CHD qualified health claims on canola oil, vegetable oil spreads, dressings for salads, shortenings and canola oil-containing foods are discussed below. FDA does not intend to exercise its enforcement discretion for any type of meal product (21 CFR 101.13(l)) or main dish product (21 CFR 101.13(m)), as none of the scientific evidence that suggested a relationship between UFAs from canola oil in replacement of SFAs and reduced risk of CHD used these types of foods.

"Total fat" disqualifying levels

In the previous section (Section IV, A), FDA explained that the agency has decided not to consider, in the exercise of its enforcement discretion, that canola oil, vegetable oil spreads, dressings for salads, shortenings, and canola oil-containing foods that bear a UFAs from canola oil and reduced risk of CHD qualified health claim meet the "low fat" criterion as defined by 21 CFR 101.62(b)(2). FDA notes that there is a large difference in the amount of total fat between the "low fat" criterion and the disqualifying total fat level. For example, the "low fat" criterion for individual foods is equal to or less than 3 g per RACC and per 50 g if the RACC is 30 g or less or 2 tablespoons or less. The disqualifying total fat level for individual foods is above 13 g per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoon or less. Thus, there is a difference of 10 g for individual foods between the "low fat" criterion and the disqualifying total fat level.

Canola oil exceeds the disqualifying total fat level because it is essentially entirely fat. However, the UFAs from canola oil and CHD qualified health claim will inform consumers that they might lower their risk of CHD by consuming foods containing UFAs from canola oil in place of similar foods high in SFAs, while not increasing caloric intake. FDA believes this type of dietary information will help consumers maintain healthy dietary practices by providing consumers with information that can facilitate reductions of saturated fat and cholesterol intake without increasing total calorie consumption. Furthermore, FDA concurs with current Dietary Guidelines for Americans, 2005, that consuming diets low in saturated fat and cholesterol is more important in reducing CHD risk than consuming diets low in total fat. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that canola oil meet the disqualifying total fat level to bear a UFAs from canola oil and CHD qualified health claim.

The most and less persuasive scientific studies that suggest a relationship between UFAs from canola oil in replacement of SFAs and reduced risk of CHD used canola oil incorporated into several types of foods that are traditionally high in fat, namely vegetable oil spreads, dressings for salads, and shortenings. Products labeled as margarine (21 CFR 166.110) must contain at least 80% vegetable oil by weight¹⁷ and shortenings are essentially all fat. Foods that contain these levels of fat will necessarily exceed the disqualifying total fat level. If FDA imposed the disqualifying total fat level on these products, it would prevent these products, which were included in the scientific studies that suggested a relationship, from bearing the claim. Canola oil-containing foods are generally not vehicles for delivering fat. However, given that FDA

¹⁷ FDA recognizes that margarine-like products do not have to meet the fat criteria as defined in the standards of identity for margarine (21 CFR 166.110).

intends to exercise enforcement discretion for canola oil products that contain 4.75 g or more canola oil per RACC, and the food may be formulated with additional canola oil and still contribute to the claimed effect, FDA concludes that applying the disqualifying levels of total fat to canola oil-containing foods would unduly limit the foods that could contribute to beneficial effects from bearing the claim. Further, FDA has concluded that foods labeled with a UFAs from canola oil and CHD qualified health claim would assist consumers in maintaining healthy dietary practices, since the claim provides consumers with information to select products that have less SFAs and more UFAs while not increasing their total caloric intake. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that vegetable oil spreads, dressings for salads, shortenings, and canola oil-containing foods that bear a UFAs from canola oil and CHD qualified health claim meet the total fat disqualifying level. However, FDA believes that it is appropriate to consider as a factor in the exercise of its enforcement discretion that when the total fat level in the food exceeds the disqualifying level as defined by 21 CFR 101.14(a)(4), the disclosure statement (i.e., See nutrition information for total fat content.) must comply with 21 CFR 101.13(h).

"Saturated fat" disqualifying level

As mentioned earlier, canola oil meets the definition of a "low saturated fat" food with a RACC of canola oil containing approximately 0.994 g of saturated fat. In meeting the requirement for "low saturated fat," canola oil also meets the disqualifying saturated fat level.

FDA intends to consider, as a factor in the exercise of its enforcement discretion for canola oil and canola oil products labeled with a UFAs from canola oil and reduced risk of CHD qualified health claim, that such products meet the disqualifying saturated fat level as specified in 21 CFR 101.14(a)(4).

"Cholesterol" disqualifying level

FDA intends to consider, as a factor in the exercise of its enforcement discretion for canola oil and canola oil products labeled with a UFAs from canola oil and reduced risk of CHD qualified health claim, that such products meet the disqualifying cholesterol level as specified in 21 CFR 101.14(a)(4).

"Sodium" disqualifying level

FDA intends to consider, as a factor in the exercise of its enforcement discretion for canola oil and canola oil products labeled with a UFAs from canola oil and reduced risk of CHD qualified health claim, that such products meet the disqualifying sodium level as specified in 21 CFR 101.14(a)(4).

C. 10 Percent Minimum Nutrient Content Requirement

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10% of the Daily Value for vitamin A, vitamin C, iron, calcium, protein, or dietary fiber per RACC (21 CFR 101.14(e)(6)). The purpose of this provision is to prevent the use of health claims on foods with minimal nutrition value.

FDA has previously exempted certain foods from the 10% minimum nutrient content requirement when it has been determined that such exemptions could assist consumers in maintaining healthy dietary practices. For example, the agency exempted spreads and dressings for salads from this requirement in the plant sterol/stanol esters and CHD health claim interim final rule (65 FR 54868 at 54711). FDA also considered a qualified health claim for walnuts and a reduced risk of CHD, even though walnuts did not meet the 10% minimum nutrient requirement (<http://www.cfsan.fda.gov/~dms/qhcnuts3.html>). Most recently, FDA exempted olive oil and olive oil-containing dressings for salads and shortenings from the 10% minimum nutrient requirement for the MUFAs from Olive Oil and CHD Qualified Health Claim (<http://www.cfsan.fda.gov/~dms/qhcolive.html>).

Canola oil, dressings for salads, and shortenings do not meet the 10% minimum nutrient content requirement of 21 CFR 101.14(e)(6). However, canola oil, dressings for salads, and shortenings provide UFAs that can be used in place of SFAs in the diet. FDA believes that information to help consumers reduce saturated fat and cholesterol consumption would assist consumers in maintaining healthy dietary practices. If FDA did impose the 10% minimum nutrient content requirement for these food categories, it would prevent these major canola oil products, which were included in the scientific studies that suggested a relationship, from bearing the claim. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that canola oil, dressings for salads, and shortenings that bear a UFAs from canola oil and CHD qualified health claim meet the 10% minimum nutrient content requirement.

Margarine (21 CFR 166.110), margarine substitutes, and margarine products labeled under 21 CFR 130.10 must contain more than 10% of the Recommended Dietary Allowance (RDA) for vitamin A and most commercially available margarine-like products also contain more than 10% of the RDA for vitamin D. Therefore, FDA intends to consider, in the exercise of its enforcement discretion, that vegetable oil spreads labeled with a UFAs from canola oil and CHD qualified health claim meet the 10% minimum nutrient content requirement.

FDA also considers it appropriate that canola oil-containing foods meet the 10% minimum nutrient content requirement. Canola oil-containing foods are generally not vehicles for delivering fat (unlike canola oil, vegetable oil spreads, dressings for salads, and shortenings) and contain many other ingredients that may contribute to or detract from a healthy diet. Thus, FDA believes that such foods should meet the 10% minimum nutrient content requirement. FDA believes that several canola oil-containing foods can be formulated to contain enough canola oil to be eligible for the claim and meet the 10% minimum nutrient content requirement. Therefore,

FDA intends to consider as a factor, in the exercise of its enforcement discretion, that canola oil-containing foods labeled with a UFAs from canola oil and CHD qualified health claim meet the 10% minimum nutrient content requirement.

D. *Trans* Fat Levels in Foods Eligible for the Claim

The petitioner requested that canola oil-containing products be required to contain no more than one gram of *trans* fatty acids per RACC. Currently, there is a lack of scientific evidence to establish a daily value for *trans* fatty acids but it is well known that *trans* fatty acids increase blood total- and LDL-cholesterol levels (IOM, 2002). FDA has issued an advanced notice of proposed rulemaking (ANPRM) to solicit comments on establishing *trans* fat nutrient content claims; to establish qualifying criteria for *trans* fat in current nutrient content claims for SFAs and cholesterol, lean and extra lean claims and health claims that contain a message about cholesterol-raising lipids; and, in addition, to establish disclosure and disqualifying criteria to help consumers make healthy food choices. The agency also solicited comment on whether it should consider statements about *trans* fat, either alone or in combination with saturated fat and cholesterol, as a footnote in the Nutrition Facts panel or as a disclosure statement in conjunction with claims (68 FR 41507; July 11, 2003). FDA intends to consider the petitioner's request, that canola oil products contain no more than 1 gram *trans* fatty acids per RACC, in the context of the agency's activities related to the ANPRM. FDA believes that it would be premature to consider, as a factor in the exercise of its enforcement discretion, a specific nutrient disqualifying level for a UFAs from canola oil and CHD risk reduction qualified health claim, until it has evaluated the merits of a level based on the data and information it is currently evaluating in the context of the ANPRM. Therefore, FDA declines the petitioner's request to consider a *trans* fat qualifying level as a factor in the exercise of its enforcement discretion for this qualified health claim.

E. Context of the total daily diet

A provision of the general requirements for health claims requires that a health claim enable the public to comprehend the information provided and to understand the relative significance of such information in the context of the total daily diet (see § 403(r)(3)(B)(iii) of the Act (21 U.S.C. § 343(r)(3)(B)(iii)) and 21 CFR 101.14(d)(2)(v)). For health claims pertaining to CHD that are authorized by regulation, FDA requires information relative to a total diet low in saturated fat and cholesterol because this is an essential part of dietary guidance for reducing the risk of CHD. However, the information in the UFAs from canola oil and CHD qualified health claim will provide consumers a method to reduce saturated fat and cholesterol intake, i.e., by consuming UFAs from canola oil and canola oil products in place of SFAs. Further, the most and less persuasive scientific studies did not suggest that the intervention diet must be low in cholesterol (< 300 mg per day) in order to reduce the risk of CHD. Thus, FDA will not consider, in the exercise of its enforcement discretion, the use of a phrase or sentence relating to diets low in saturated fat and cholesterol.

F. Minimum Effective Amount of Canola Oil in Foods Eligible for the Claim

The general requirements for health claims require that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in the appropriate form to justify the claim. Where no definition of high has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)).

The agency determined the minimum effective amount of UFAs from canola oil necessary to substitute in place of SFAs by first calculating the difference in the amount of UFAs, in grams,¹⁸ between the high-UFA and high-SFA diets in the three strictly controlled intervention studies that demonstrated a reduction in serum total- and LDL-cholesterol levels. This limited evidence suggests that the lowest amount of UFAs needed to replace SFAs that may result in significant reduction in serum total- and LDL-cholesterol is 17.7 g of UFAs (Wardlaw et al., 1991). Canola oil contains approximately 92.9% UFAs (USDA Nutrient Database for Standard Reference, Release 18). Consuming 19 g of canola oil per day provides 17.7 g of UFAs. Nineteen grams of canola oil is equivalent to approximately 1.5 tablespoons. The RACC for canola oil is one tablespoon, which contains approximately 12.4 g of UFAs and 1 g of SFAs.

To determine the minimum amount of canola oil necessary to be in a food, the agency considered the number of eating occasions at which consumers might consume canola oil or canola oil products and the number of potential foods that could be labeled with a qualified health claim about UFAs from canola oil and CHD. Foods in these categories can be part of every eating occasion, and the typical American eating pattern is three meals and one snack per day. Therefore, the determination of the qualifying level of UFAs from canola oil for a food to bear the claim will be based on four eating occasions per day. The minimum effective dose (19 g canola oil per day) based on four eating occasions per day of canola oil or the four categories of canola oil-containing products is 4.75 g of canola oil per RACC per day. For consumers to know the amount of canola oil in a product, FDA intends to consider, in the exercise of its enforcement discretion, that foods that bear a UFAs from canola oil and CHD qualified health claim state the amount of canola oil per serving in the claim.

V. Conclusions

Based on FDA's consideration of the scientific evidence submitted with your petition, and other pertinent scientific evidence, FDA concludes that there is sufficient evidence for a qualified health claim, provided that the claim is appropriately worded so as to not mislead consumers. Thus, FDA intends to consider exercising enforcement discretion for the following qualified health claim:

"Limited and not conclusive scientific evidence suggests that eating about 1 ½ tablespoons (19 grams) of canola oil daily may reduce the risk of coronary heart disease due to the unsaturated

¹⁸ The amount of UFAs in grams was calculated by multiplying the percent of energy by 2000 kcal and converting to grams.

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fat content in canola oil. To achieve this possible benefit, canola oil is to replace a similar amount of saturated fat and not increase the total number of calories you eat in a day. One serving of this product contains [x] grams of canola oil."

The appropriate disclosure statement "See nutrition information for total fat content." must be included on the label and comply with 21 CFR 101.13(h).

FDA intends to consider exercising enforcement for the above qualified health claim when all other factors for enforcement discretion identified in Section IV of this letter are met. Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement or that will no longer support the use of a qualified health claim, or that raises safety concerns about that substance that is the subject of the claim.

Sincerely,



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U.S. Department of Health and Human Services (HHS) and U.S. Department of Agriculture (USDA), *Dietary Guidelines for Americans, 2005*.

Appendix 1

Please see Docket No. 2006Q-0091, QHC1, for the following studies:

Duration of intervention period to short (less than 3 weeks)

Chan et al., 1991

Hodson et al., 2001

McDonald et al., 1989

Kratz et al., 2002

Kratz et al., 2002

Kratz et al., 2003

Truswell et al., 1992

Mutanen et al., 1992

Valesta et al., 1992

No comparison saturated fat group

Becker et al., 1999

Chan et al., 1991

Gylling et al., 1999

Jenkins et al., 1997

Li et al., 1998

Nydahl et al., 1995

Freese et al., 1994
Guiesserian et al., 2002
Gustafsson et al., 1994
Metcalf et al., 2003
Miettinen et al., 1994
Nielsen et al., 2002
Nydahl et al., 1994
Pedersen et al., 2000
Seppanen-Laakso et al., 1992
Seppanen-Laakso et al., 1993
Turpeinen et al., 1995
Valsta et al., 1995

Source of unsaturated fatty acids was not solely from canola oil

Luscombe et al, 1999
Metcalf et al., 2003
Muller et al., 2003
Smith et al., 2003
Howard et al., 1995

Republication

Lichtenstein et al., 1994
Jones et al., 1994
Valasta et al., 1996

No validated endpoint for measuring coronary heart disease

Freese et al., 1994
Metcalf et al., 2003
Kratz et al., 2002
Kratz et al., 2003
Turpeinen et al., 1995

Subjects diagnosed with coronary heart disease

Herrmann et al., 1995