THE SCIENTIFIC EVIDENCE AND APPROACH TAKEN TO ESTABLISH GUIDELINES FOR CHOLESTEROL INTAKE IN AUSTRALIA, CANADA, THE UNITED KINGDOM, AND THE UNITED STATES

November 2006

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LSRO Report: Approach to Establish Guidelines for Cholesterol Intake

Cover graphic: Canadian Egg Marketing Agency
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Editor’s Note:

For further information about this study, see *The Scientific Evidence and Approach Taken to Establish Guidelines for Cholesterol Intake in Australia, Canada, the United Kingdom, and the United States* at: http://www.LSRO.org
FOREWORD

The Life Sciences Research Office, Inc. (LSRO) provides scientific assessments of topics in the biomedical sciences. LSRO reports are based on comprehensive literature reviews and the scientific opinions of knowledgeable investigators who work in relevant areas of biology and medicine.

This LSRO study, *The Scientific Evidence and Approach Taken to Establish Guidelines for Cholesterol Intake in Australia, Canada, the United Kingdom, and the United States*, was initiated by The American Egg Board (AEB), 1460 Renaissance Drive, Park Ridge, Illinois 60068, in accordance with a contract between LSRO and AEB.

This report summarizes the publicly available scientific evidence and methods used to establish dietary guidelines for the intake of cholesterol that were based on the relationship of diet and heart disease. LSRO reviewed the evidence and methods used to set the current U.S. dietary guidelines for cholesterol intake and compared and contrasted these with approaches taken by Canada, Australia, and the United Kingdom. LSRO staff considered all available information when drafting the report, considered reviewers’ comments, and provided additional documentation and viewpoints for incorporation into the final report.

LSRO independently recruited expert reviewers according to their qualifications, experience, and judgment, with due considerations for balance and breadth in the appropriate professional disciplines. The expert reviewers and others who assisted in the preparation of the report are identified in the report. Reviewers of the draft report provided suggested edits and comments, some of which were incorporated. They were not asked to review or endorse the final report.

The final report was reviewed and approved by the LSRO Board of Directors. On completion of these review procedures, the Executive Director of LSRO approved and transmitted the report to AEB. LSRO is solely responsible for the content of this report. This report was developed independently, and the conclusions drawn herein do not necessarily reflect the views or policies of AEB or of any of its employees. Although LSRO accepts full responsibility for the study conclusions and accuracy of the report, the report does not necessarily represent the opinion of the LSRO Board of Directors. The mention of trade names, commercial products, or organizations does not imply endorsement by LSRO.

*Michael Falk, Ph.D.*
*Executive Director, Life Sciences Research Office, Inc.*
*November, 2006*
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EXECUTIVE SUMMARY

BACKGROUND

Prominent public health and medical groups have invested considerable time and attention in reviewing evidence relating dietary cholesterol and blood lipids to cardiovascular health, and in translating their evaluations into recommendations for dietary intake of cholesterol for the general U.S. population. These recommendations have led to public health policy initiatives and education campaigns influencing the American diet. However, the relevance of dietary cholesterol as a primary target for public health programs and disease prevention has been questioned by some experts.

The most commonly eaten foods contributing cholesterol to the diet are meats, eggs, and cheese. Data on the cholesterol content of food have been available for many years but have been revised as analytical methods and equipment improved. A value of 274 mg cholesterol per 50-gram egg was in use by the United States Department of Agriculture (USDA) in the 1970s (Posati & Orr, 1976). Analysis of eggs from a nationwide sampling in 1988–1989 yielded an average value for cholesterol of 213 mg per 50-gram egg. Still another nationwide sampling, in 2001–2002, yielded the current value of 212 mg per 50-gram egg (U.S. Department of Agriculture, 2006c). Recalculation of the cholesterol content in foods containing eggs as ingredients would have occurred within a year or two after the egg values from 1988–1989 were reported. Similarly, the cholesterol content reported by USDA for cholesterol-containing non-egg foods declined substantially during this period. Hence, dietary intake data from studies vary over time with respect to the calculation of cholesterol content, not because actual cholesterol content of food decreased appreciably, but because of improvements in the analytical techniques and increasing use of standard reference materials to verify precision and analytical accuracy.

The American Heart Association (AHA) Committee on Nutrition (1968) set the first U.S. threshold for cholesterol intake at 300 mg/d for hypercholesterolemic patients. This limit was based on several intervention studies showing that a modified diet, which included limiting dietary cholesterol to less than 300 mg/d, could reduce blood total cholesterol in most (but not all) persons having elevated blood concentration (American Heart Association Committee on Nutrition, 1968; Page & Stamler, 1968b). This recommended limit was extended to the general population two years later by the Inter-Society Commission for Heart Disease Resources (1970), whose work had been contracted by AHA, in an attempt to cut in half the estimated 600 mg/d average U.S. daily intake. This commission was encouraged by findings from three primary prevention trials that restricted dietary saturated fat and cholesterol and increased intake of polyunsaturated fat, resulting in lower blood total cholesterol and decreased incidence of coronary events, but not mortality.

At least 30% of U.S. men surveyed in 1994–1996 exceeded recommendations for daily cholesterol intake, while average intakes by women, girls, and boys under 12 years of age tend to comply with recommendations (Dixon & Ernst, 2001). Food survey data collected through 1998 indicate that males over 12 years of age are consuming, on average, more than 320 mg/d of cholesterol (Dixon & Ernst, 2001).
THE STUDY

The American Egg Board sought to understand why consensus committees with access to the same published literature reach different conclusions and construct different recommendations for cholesterol intake. It contracted with the Life Sciences Research Office, Inc. (LSRO), to provide an independent review of the publicly available scientific evidence and methods used to establish dietary guidelines for the intake of cholesterol that were based on the relationship of diet and heart disease.

LSRO compiled public health guidelines for cholesterol intake issued by the World Health Organization (WHO), the United States, Canada, the United Kingdom, and Australia, and attempted to describe the processes and key evidence used by the national health councils to arrive at these guidelines. The scope of the review was limited to that data cited by recommending bodies. LSRO conducted this study in conjunction with independent, multidisciplinary expert scientists, who reviewed this report.

This LSRO report pertains to population-based public health approaches for disease prevention and does not delve into medical strategies for treatment of at-risk individuals, except for those data relevant to the development of public policy. LSRO did not undertake an evaluation of the scientific literature for the purpose of validating the appropriateness of current dietary recommendations or of suggesting alternative recommendations.

RECOMMENDATIONS AND SUPPORTING EVIDENCE

U.S. Dietary Reference Intakes

In its report *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2005a) the Institute of Medicine (IOM) Food and Nutrition Board reviewed data regarding the association of dietary cholesterol and cardiovascular disease. It examined three main lines of evidence: animal models, epidemiological data, and the effects of dietary cholesterol on blood lipoproteins in human clinical trials.

IOM recognized that experimental data in several animal species provided evidence that dietary cholesterol can induce atherosclerosis but decided that marked differences in cholesterol metabolism between species negated the extrapolation of data directly to humans.

IOM then reviewed 15 epidemiological reports on the effects of dietary cholesterol on heart disease. Six of these reports indicated a positive relationship between cholesterol intake and cardiovascular disease and/or biomarkers of coronary heart disease (CHD), such as carotid artery wall thickness. But because of the limited power of epidemiological studies to detect the 1% to 2% increase in CHD estimated from changes in dietary cholesterol, IOM (2005a) concluded that existing epidemiological data “did not provide a meaningful basis for establishing adverse health effects of dietary cholesterol.”

IOM used the effects of dietary cholesterol on blood lipoproteins as the basis for its conclusions regarding the association of dietary cholesterol and cardiovascular disease. IOM cited Hegsted *et al.* (1993) as suggesting that changes in low density lipoprotein (LDL)-cholesterol “roughly parallel” and “approximate” changes in blood total cholesterol. IOM further stated that approximately 80% of the increase in blood total cholesterol (in response to changes in dietary
cholesterol) is in the LDL fraction, an estimate that although not specifically cited is consistent with IOM’s discussion of Clarke et al. (1997).

IOM also reviewed 50 clinical studies examining the lipoprotein response to dietary cholesterol. In these studies, the effects of cholesterol intake ranging from 0 to 585 mg/d were compared to effects after supplementing these diets with additional cholesterol in amounts ranging from 7 to 4800 mg/d. IOM (2005a) concluded that there was a positive linear trend between cholesterol intake and blood cholesterol concentration.

Most of the studies reviewed by IOM tested responses at extremely high cholesterol intakes; less than one-half included measures of blood cholesterol associated with changing dietary cholesterol by 500 mg/d or less. According to IOM (2005a), none of the studies it reviewed examined the effects of very small incremental changes in dietary cholesterol in sufficiently large enough samples to permit statistical treatment of the data to define the lowest level of cholesterol intake shown to increase total- or LDL-cholesterol concentration (i.e., the lowest-observed-adverse-effect level). Based on the risk assessment model, IOM was unable to derive a Tolerable Upper Intake Level for cholesterol because neither a no-observed-adverse-effect level nor a lowest-observed-adverse-effect level could be determined. It concluded, “any incremental increase in cholesterol intake increases CHD risk.” Thus in its report, IOM (2005a) recommended that cholesterol consumption be “as low as possible while consuming a nutritionally adequate diet.”

U.S. Dietary Guidelines

Current dietary guidelines are based on the accumulated body of scientific work to date. The most recent federal compendium on dietary cholesterol and health, Nutrition and Your Health: Dietary Guidelines for Americans (Guidelines), recommends that individuals in the general U.S. public limit their intake of cholesterol to less than 300 mg/d and that those with elevated LDL-cholesterol limit their intake to less than 200 mg/d (U.S. Department of Agriculture, 2005e).

To produce the Guidelines, a scientific report was prepared by the Dietary Guidelines Advisory Committee (DGAC). DGAC experts in nutrition and health were tasked with reviewing the then-current edition of dietary guidelines (U.S. Department of Agriculture, 2000b) and determining if, on the basis of the preponderance of current scientific and medical knowledge, any revision was warranted.

A substantial amount of the scientific information reviewed by DGAC was based on the first version of the IOM report (2002), particularly IOM’s review of 50 controlled trials and 15 observation studies. DGAC also conducted food-modeling exercises with diets varying in energy and food group restrictions (e.g., lacto-ovo vegetarian diet) to identify food choices that might be necessary both to comply with guideline recommendations and to meet nutrient needs. DGAC calculated that the lowest recommended cholesterol intake in a lacto-ovo vegetarian diet that met energy and essential nutrient recommendations would be 160 to 212 mg/d (U.S. Department of Agriculture, 2005d). Also through modeling exercises DGAC learned that dietary

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1 “Low” was not quantified.
patterns at energy levels of 2,800, 3,000, and 3,200 kcal/d contained, respectively, 310, 314, and 319 mg/d of cholesterol (U.S. Department of Agriculture, 2005b).

DGAC also examined the evidence-based review of cholesterol in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (National Heart, Lung, and Blood Institute, 2002), considered recommendations of the American Diabetes Association (Franz et al., 2004), and included five recent but unidentified controlled trials in its review (U.S. Department of Agriculture, 2005d).

DGAC did not explain its decision to reiterate the 2000 Guidelines recommendation of limiting cholesterol intake to 300 mg/d, but given its approach, DGAC likely concluded there was a lack of convincing evidence that some other value was more beneficial and feasible. DGAC cautioned that for diets providing more than 30% of calories from fat (i.e., energy intakes of 2800 kcal/d or greater), particular attention must be paid to keeping cholesterol intake at or below the recommended limit of 300 mg/d.

Specification of the cut-off value of 200 mg/d for hypercholesterolemic individuals was not explained by DGAC, but was likely adopted from similar cut-offs advocated by NCEP and the American Diabetes Association (Franz et al., 2004), whose reports were cited by DGAC.

RECOMMENDATIONS BY OTHER NATIONS AND THE WORLD HEALTH ORGANIZATION

The guidelines of Canada; Australia; the Department of Health, London; and The Scottish Office do not specifically limit dietary cholesterol. Rather, the primary fat-related dietary objectives of these countries focus on reducing saturated fats and lowering the average total fat intake. The following paragraph by the European Heart Network (2002) is typical of the line of reasoning of countries that have chosen to omit a specific goal for dietary cholesterol:

Cholesterol in the diet increases LDL-cholesterol levels in the blood, but to a much lesser extent than saturated fat, and the response varies widely among individuals. Foods high in cholesterol are usually also high in saturated fat, so that reducing intakes of saturated fat, as described previously, should lead to an accompanying fall in cholesterol intakes. Although there is some evidence of a relationship between cholesterol consumption and cardiovascular disease (Weggemans et al., 2001), no population goal is included because dietary cholesterol intakes in Europe tend to be within the usual population goal of less than 300 mg per day specified by expert groups and consensus documents.

Canada

Health Canada is the Canadian counterpart of the U.S. Department of Health and Human Services. Its mandate is to reduce the incidence of disease, particularly cardiovascular disease, which is the leading cause of death in Canada.

As in the United States, Dietary Reference Intakes (DRI), form the basis for Canadian dietary guidance documents. Canada and the United States share the effort to produce and update the IOM DRI. Thus, DRI represent progress toward a harmonized North American standard (Health Canada, 2005).
Canada’s food guide, issued in 1992, does not directly address cholesterol intake, and Health Canada does not require that food labels specify a reference value for cholesterol intake. A background document for educators and communicators stated, “From a dietary perspective, the key strategy for controlling blood cholesterol is to reduce the intake of total fat and, specifically, saturated fat. Dietary cholesterol, or the cholesterol found in foods, is not the main influence on blood cholesterol level, although it has some effect, in some people” (Health Canada, 2004). Recently, Health Canada undertook a revision of its food guide because research had shown that Canadians misinterpret and misapply some recommendations. An external Food Guide Advisory Committee was created to provide advice to Health Canada throughout the revision process. The draft food guide is currently evolving based on input from consultations, consumer focus testing, and regional meetings conducted early in 2006. The new food guide will extend the ages of applicability to Canadians two years of age and older; its release is anticipated sometime late in 2006 or early in 2007 (Health Canada, 2006).

**United Kingdom**

Prompted by the British Egg Information Service (BEIS), an industry trade group, the Secretariat of the Science Advisory Committee on Nutrition (SACN) considered evidence to decide whether or not to alter its advice on egg intake. Evidence reviewed included AHA recommendations and recent reviews, only one of which was identified (Weggemans et al., 2001). After discussion with the Chairman of SACN, the Secretariat responded to BEIS indicating the 1994 Committee on Medical Aspects of Food Policy recommendation “that average dietary intake of cholesterol should not rise” to still be valid. The SACN members agreed with the Secretariat’s response to BEIS (Science Advisory Committee on Nutrition, 2001).

In June 2002, SACN discussed revised recommendations made by the Subgroup on Risk Assessment for the types of evidence SACN should consider when evaluating the relationships between food, nutrients, and health. SACN (2006; 2001) recommended that in the future, evidence should be presented in a systematic and transparent way, allowing judgments to be made on both the quantitative and qualitative aspects of the included studies. Future reviews should cover the appropriateness of statistical methods, confounding factors, and the consistency of meta-analytical results. SACN noted that it would also take into account any existing U.K. public health policies for any issue under review.

The most recent dietary recommendations of The Scottish Office (2005b) and the Department of Health, London (2005), do not mention cholesterol. Rather, objectives focus on reducing saturated fats and lowering the average total fat intake.

**Australia**

The National Health and Medical Research Council of Australia (NHMRC) assembled an expert Working Party to develop the latest edition of Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes (National Health and Medical Research Council, 2006a). The Working Party was assigned to review each U.S./Canadian DRI recommendation, including that for cholesterol (Institute of Medicine, 2002) and recommend either adoption, adoption with minor changes, adoption with substantial changes, or rejection for use in Australia and New Zealand (National Health and Medical Research Council, 2006b). Other than to mention that dietary cholesterol was not essential and that this finding was in agreement with IOM, neither the specific IOM recommendation nor any other discussion of
dietary cholesterol was included in the final report (National Health and Medical Research Council, 2006b).

NHMRC’s position on dietary cholesterol is that, at the public health level, advice to reduce saturated fat will bring with it lower cholesterol intakes since these two lipid classes usually occur in the same foods. Moreover, the cholesterol-elevating effect of dietary cholesterol is considered less consistent than that of saturated fats. The reviewer who evaluated the evidence to update the adult guideline cited papers by Beynen & Katan (1989) and Bronte-Stewart (1958), several controlled experiments and meta-analyses (Clarke et al., 1997; Hegsted et al., 1965; Hegsted et al., 1993; Keys et al., 1957; Mensink & Katan, 1992), and position statements on dietary fats by the National Heart Foundation (1999a; 1999b) as supporting the appropriateness of the focus on saturated fat, in that saturated fat is the strongest dietary determinant of LDL-cholesterol.

Because many foods with a significant fat content are rich in nutrients, the reviewer who evaluated the evidence to update the pediatric guideline was particularly concerned over the safety of diets designed to overly limit consumption of fat and cholesterol in growing children because such practices have led to growth failure (Lifshitz & Moses, 1989). As far as the final consumer message, the pediatric guideline, “Limit saturated fat and moderate total fat intake” was the same as the corresponding adult guideline, except for the additional qualifier, “Low-fat diets are not suitable for infants.”

World Health Organization

A joint WHO/Food and Agricultural Organization (FAO) (2003) expert technical report on diet, nutrition, and prevention of chronic disease concluded that high intake of dietary cholesterol may lead to increased risk for CHD and recommended limiting the population (average) intake of dietary cholesterol to less than 300 mg/d. It did not provide a rationale for this specific value, but did cite the AHA Nutrition Committee report by Kris-Etherton et al. (2001), which mentioned that current dietary guidance for individuals was to keep cholesterol intake less than 300 mg/d. Yet, later WHO/FAO efforts that considered this expert technical report as well as input from numerous stakeholders produced a document describing a global strategy for diet, physical activity, and health that did not make recommendations for dietary cholesterol (World Health Organization, 2004). In its latest dietary advisory, WHO (2004) recommends that both populations and individuals “limit energy intake from total fats and shift fat consumption away from saturated fats to unsaturated fats and towards the elimination of trans-fatty acids.”

SUMMARY

In recent years, the various expert committees assembled to develop dietary recommendations for cholesterol intake have primarily used formal methods of analysis of scientific evidence along with expert opinion. Technical reports resulting from these efforts have informed federal regulators responsible for establishing or up-dating national dietary guidelines. Typically, proposed guidelines are not finalized until comments submitted by the public, industry, and other stakeholders are also considered. Technical supporting materials tend to be made publicly available along with the consumer-oriented guidance documents, and often, but not always, these documents describe the process leading to the dietary guideline and cite the evidence upon which the guideline was based.
Among the current national and international guidelines reviewed in this LSRO report, all agree on the necessity to reduce saturated fat but dietary guidelines in the United States are the only ones that also recommend a quantitative threshold for cholesterol intake. The complexity involved in constructing national guidelines for dietary intake may contribute to differences in recommendations among nations, particularly with respect to the acceptability of foods and the psychological, social, and cultural issues that affect food preference (Cooper & Zlotkin, 2003). In practical terms, the United States has food product labels specifying a Daily Value of at most 300 mg (in place since 1995), and any change in U.S. guidelines for cholesterol intake would have to coordinate these messages. In the minds of U.S. regulators and the expert panels that inform them, scientific evidence to date has not justified replacing or omitting the 300 mg/d cut-off for the general public. In fact, based on U.S. clinical guidelines, the U.S. dietary guidelines now recommend an even more stringent limit of 200 mg/d for those with elevated LDL-cholesterol.

Given the differences in time when recommendations for Australia, Canada, and the United Kingdom were last issued, spanning 1992 through 2005, it appears that accumulating data on the relationship between diet and cardiovascular health have failed to rise to a level that would prompt these countries to recommend restricting cholesterol as a key public health strategy to lower blood cholesterol.

Regulators in the United States and Canada rely upon IOM reports to provide a comprehensive and up-to-date review of the scientific evidence for the relationship between dietary cholesterol and chronic disease to inform their decisions in setting national dietary guidelines for cholesterol intake. It will be of interest to see whether the IOM’s inability to quantify a no-observed-adverse-effect level for cholesterol intake will influence the new Canadian dietary guidelines, which are due within six months (Institute of Medicine, 2005b). Preliminary food modeling exercises conducted by USDA suggest that healthy food patterns for lacto-ovo vegetarians contain approximately 160 to 212 mg/d of cholesterol, depending on energy requirements, helping to define what “low” intakes might be possible (U.S. Department of Agriculture, 2005c). The next issue of the U.S. dietary guidelines is planned for 2010.

Next steps

Fortunately, blood lipid concentrations have been declining substantially in the United States, and there has been a decline in coronary heart disease (CHD) in the United States and other countries as well. The amount and types of dietary fats consumed affect the risk of atherosclerosis and CHD, but questions remain as to the most heart-healthy mix of dietary fats for the general population. Research on the health benefits and risks of the different types of fat and food ingredients may provide support for new consumer messages and trickle-down effects in industry that will deliver greater health benefits than do the current dietary guidelines. For example, can it be determined which saturated fats are most atherosclerotic and can these be decreased in the food supply? How will increasing polyunsaturated fatty acids, especially omega-3 fatty acids from plants and fish, alter the risk of CHD?

The reports of the INTERLIPID (Ueshima et al., 2003) and INTERMAP (Zhou et al., 2003) studies are raising interesting hypotheses regarding eating patterns and very high consumption of cholesterol in the diet among Japanese in Japan compared with samples in the United States or the United Kingdom. The Japanese diet is typically high in cholesterol (446 mg/d among men and 359 mg/d among women) and omega-3 fatty acid, yet is lower in total fat and in saturated fat.
than diets in Western industrialized countries (Ueshima et al., 2003; Zhou et al., 2003). This population has relatively low body weight, relatively lower LDL-cholesterol and lower risk of CHD comparable to the U.S. and U.K. populations, but higher risk of stroke (Ueshima et al., 2003; Zhou et al., 2003).

Dietary guidelines must be based on the average population, presuming varying susceptibilities within the population. IOM determined that more information is needed on the contributing factors in individual variation of LDL-cholesterol response to dietary cholesterol (i.e., genetic variants and non-cholesterol components of diet).

Overall, the majority of studies on the health aspects of dietary cholesterol and blood cholesterol are of adults. Further research is needed to better define optimal blood cholesterol concentrations and cardiovascular risk factors for healthy children, particularly with regard to biological age (pubertal status), sex-related differences, and weight status (Viikari et al., 2004; Wang et al., 2005; Wennlof et al., 2005). Further research is needed to determine the optimal dietary fat composition during childhood to minimize long-term risk for CHD while supporting healthy growth and development (Ong et al., 2006). Such studies will inform school feeding programs and other public health activities and are especially important given the rise in pediatric obesity and pediatric type II diabetes, which increase risk of cardiovascular diseases. In 1999-2000, peak intake of 375 mg/d of cholesterol in boys was reached between 16 to 19 years of age. Among males age 12 to 19 years, the mean (but not median) cholesterol intake exceeded 300 mg/d regardless of racial/ethnic group. Should targeted efforts be undertaken to reduce the intake of dietary cholesterol in these groups and better understand the quantitative relationship between lowering dietary cholesterol or saturated fat intake and blood total or LDL-cholesterol in adolescence?

Research that explores the effects of very small incremental changes in dietary cholesterol to define the lowest level of cholesterol intake shown to increase total or LDL-cholesterol concentration might be beneficial for defining a threshold for cholesterol intake. To complement these efforts, further food modeling studies by USDA could provide information that might assist in creating sample healthy food patterns and planning nutritious diets containing “low” amounts of dietary cholesterol.

Finally, dietary guidelines should remain evidence-based and be modified consistent with advances in science, particularly as our understanding of the mechanisms of pathogenesis of CHD improves and new biomarkers of disease are identified. A direct assessment of the validity of the cholesterol dietary guidance documents is needed to determine whether recommended levels of cholesterol intake result in reduced levels of the biomarkers of disease (i.e., LDL-cholesterol) and contribute to reductions in CHD. Barter et al. (2006) proposed that measures of apolipoprotein B (apo B) are more informative than LDL-cholesterol as an index of the risk of cardiovascular events. If a change takes hold to adopt apo B, the apo B/apo A-I ratio, and the number of LDL particles as biomarkers for CHD risk, it will propel us to question what dietary factors, if any, influence them and minimize the risk of cardiovascular disease.
I. INTRODUCTION

I.1 SCOPE OF WORK

I.2 BACKGROUND

I.2.1 Cholesterol
I.2.2 Dietary cholesterol
I.2.3 Dietary guidelines
I. INTRODUCTION

Several governmental agencies issue recommendations for cholesterol intake with the intention of reducing the incidence of disease and promoting overall public health. But multiple, sometimes conflicting recommendations may be confusing to the general public and health professionals (Dwyer, 2006). In this report, the Life Sciences Research Office, Inc. (LSRO) compiled current national and international public health recommendations for cholesterol intake and described the processes and key evidence used to arrive at these recommendations. The report identifies areas of general agreement among the scientists who inform public health policy makers and also discusses differences in the public health messages concerning dietary cholesterol and cardiac health.

I.1 SCOPE OF WORK

The objectives of this report are to summarize the evidence and methods used to set the current U.S. dietary guidelines for cholesterol intake, and to compare and contrast these with approaches taken by Canada, Australia, and the United Kingdom. The primary focus is on describing the evidence underpinning national recommendations for cholesterol intake and the various interpretations of this evidence based on the relationship of diet and heart disease. LSRO does not intend to judge the recommendations themselves; instead, it seeks to understand the key factors upon which various national health councils based their decision whether or not to set levels of recommended cholesterol intake. The effect of dietary cholesterol on risk factors for coronary heart disease (CHD) will therefore be discussed in the context of U.S., Canadian, Australian, and U.K. recommendations.

To accomplish these objectives, LSRO staff searched the published literature regarding the development of national dietary guidelines, authored the LSRO report, and managed the process of document generation and final report preparation with due regard for scientific objectivity, completeness, and freedom from conflict of interest on the part of all participants. Biographical summaries for study participants are provided in Appendix A.

This LSRO report was subjected to an independent review by ad hoc experts selected by LSRO from a group of qualified candidates. These scientists were identified and contacted by LSRO for their combined knowledge of (1) diet and lifestyle determinants of CHD and prevention, (2) biochemical risk factors for CHD, (3) epidemiology of blood lipids, cholesterol intake, and CHD, (4) dietary guideline development and public health recommendations for cholesterol intake, and (5) research and editorial skills. To ensure an independent review, LSRO obtained conflict of interest disclosure statements from these expert reviewers and verified that they: (a) were not currently developing/promoting projects funded by the American Egg Board or the Egg Nutrition Center, and (b) their current research is not supported by the American Egg Board or the Egg Nutrition Center.

The author reached a definitive conclusion on the approach taken by leading national policy organizations with regard to the data to support guidelines for cholesterol intake and heart disease. The research gaps identified in the course of this review are documented. The differences in interpretation by leading national policy organizations in the United States, Canada, the United Kingdom, and Australia are included in the report.
LSRO was asked to synthesize and summarize the scientific evidence reviewed by various
national health councils and consensus groups, including the key factors upon which they based
their decision to set or not to set levels of recommended cholesterol intake. LSRO did not
undertake a comprehensive up-to-date evaluation of the literature.

I.2 BACKGROUND

I.2.1 Cholesterol

Cholesterol (C_{27}-H_{45}-OH) (Figure I.1) is a natural substance made by animal tissue. Plants
generally contain only small quantities of cholesterol (Behrman & Gopalan, 2005). In adult
humans, endogenous cholesterol synthesis averages 12 to 13 mg/kg body weight per day (e.g.,
840 to 910 mg/d for a 70-kg individual) (Di Buono et al., 2000).

Cholesterol is necessary for the formation, structure, and function of cell membranes. It is also
essential for normal development of the brain and nervous tissue. Cholesterol serves as the
precursor for bile acids, which are synthesized in the liver and secreted into the gastrointestinal
tract (via the gallbladder) to help digest dietary fats. In skin, cholesterol serves as the precursor
for synthesis of vitamin D in response to sunlight. Similarly, cholesterol is the precursor for
production of steroid hormones, such as estrogen, testosterone, and aldosterone.

Under normal circumstances, much of the endogenous cholesterol secreted into the
gastrointestinal tract during digestion is reabsorbed (as part of the process of enterohepatic
circulation) along with the cholesterol obtained from food.

Because the human body can produce sufficient amounts of cholesterol to meet its needs, there is
no minimum intake required. Individuals who abstain from all animal foods (vegans) can have a
nutritionally adequate diet with proper planning, which may include intake of fortified and
supplemented foods to include vitamin D, vitamin E, vitamin B_{12}, calcium, potassium, iron and
iodine (American Dietetic Association & Dietitians of Canada, 2003; Appleby et al., 1999).

Blood cholesterol

Cholesterol is transported through the blood in the form of cholesteryl esters in lipoproteins.
Low density lipoproteins (LDL) contain at least 60% of the blood cholesterol and high density
lipoproteins can carry an additional 20% to 30% of blood cholesterol (National Research
Council, 1989a). Early epidemiological studies included measures of total cholesterol but did
not measure LDL-cholesterol because of technical difficulty and cost (National Research
Council, 1989a). Currently, LDL-cholesterol is used as a primary target of cholesterol-lowering
therapy because it has consistently exhibited a strong relationship to individual and population risk of CHD (National Research Council, 1989a).

Total blood cholesterol is measured in both serum and plasma; concentrations in serum are about 2% to 3% higher than those measured in plasma (American Heart Association Committee on Nutrition, 1978; National Research Council, 1989a). In the United States, blood cholesterol is reported in mg/dL whereas in Canada and elsewhere it is reported in mmol/L. To convert plasma cholesterol in mg/dL to mmol/L, multiply mg/dL by 0.02586 and report value to the nearest 0.05 mmol/L (Young, 1990).²

Blood total cholesterol typically rises with age. For example, the 50th percentile of serum total cholesterol concentration of U.S. women in the National Health and Nutrition Examination Survey (NHANES) III was 181 mg/dL for individuals 20 to 34 years of age, 212 mg/dL for individuals 45 to 54 years of age, and 232 mg/dL for individuals 65 to 74 years of age (National Heart, Lung, and Blood Institute, 2002). In addition to age, other factors that alter rates of biosynthesis and/or enterohepatic uptake (e.g., genetic differences) and dietary factors that interfere with cholesterol absorption can influence blood levels of cholesterol.

Vegans tend to consume less saturated fat and greater amounts of dietary fiber than omnivores (Appleby et al., 1999; Krajcovicová-Kudlacková et al., 2000). Such differences in diet contribute to vegans having significantly lower blood total cholesterol and LDL-cholesterol concentrations compared to omnivores (Appleby et al., 1999; Fisher et al., 1986; Krajcovicová-Kudlacková et al., 2000). Among 114 U.K. vegans who were less than 70 years of age, mean±SE total cholesterol and LDL-cholesterol were 4.29±0.140 mmol/L (165.9±5.4 mg/dL) and 2.28±0.126 mmol/L (88.2±4.9 mg/dL; 53% of total), respectively; data were adjusted for age and sex for comparison to meat-eaters (Appleby et al., 1999).

### 1.2.2 Dietary cholesterol

#### Sources of dietary cholesterol

Data on the cholesterol content of food have been available for many years and have been revised as analytical methods and equipment improved. New gas chromatographic techniques with improved precision can distinguish cholesterol from other sterols, which result in lower values for cholesterol content compared with results obtained from earlier colorimetric methods. Prior to January 1989 scientists lacked standard reference material to verify the accuracy of their analyses.

Changes in the reported cholesterol content of eggs over time are an example of how analytical improvements have changed food composition tables. A value of 274 mg cholesterol per 50-gram egg was reported in Section 1 of the 1976 U.S. Department of Agriculture (USDA) Handbook 8-1, *Composition of Foods, Dairy and Egg Products* (Posati & Orr, 1976). This average was based on 133 values from multiple sources. Analysis of eggs from a nationwide sampling in 1988–1989 yielded an average value for cholesterol of 213 mg per 50-gram egg (n = 33). Still another nationwide sampling, in 2001–2002, yielded the current value of 212 mg (4% of total fat) per 50-gram egg (n = 23) (U.S. Department of Agriculture, 2006c). One raw, boiled, or poached large egg (50 g) contains 5 g of total fat, including 1.6 g of saturated fat, almost all of

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² To convert total cholesterol mmol/L to mg/dL, multiply mmol/L by 38.6698.
which is located in the yolk (U.S. Department of Agriculture, 2006c). More than 90% of the lipids in yolk are in the form of triglyceride or phosphatidylcholine with the remainder consisting of cholesterol and other lipids (Kovacs-Nolan et al., 2005).

The recalculation of the cholesterol content in foods containing eggs as ingredients occurred a year or two after the egg values from 1988–1989 were reported. Similarly, the cholesterol content reported by USDA for cholesterol-containing non-egg foods declined substantially during this period. Because the most concentrated naturally-occurring sources of cholesterol are in organ meats, egg yolks, and shellfish, the reported cholesterol content values for these foods showed the steepest decline over time.

Although cholesterol is a type of fat, the total fat content of a food does not necessarily reflect its cholesterol content. Intake of dietary cholesterol has been correlated, albeit weakly, with intake of saturated fat in food ($r = 0.31$) (Hegsted, 1986). But foods that are rich in cholesterol are not necessarily rich in saturated fat, or vice versa (Table I-1).

### Table I-1. A comparison of the cholesterol and saturated fat content of example foods rich in these fats (U.S. Department of Agriculture, 2006b; U.S. Department of Agriculture, 2006c).

<table>
<thead>
<tr>
<th>Food item</th>
<th>Weight (g)</th>
<th>Common measure</th>
<th>Cholesterol (mg)</th>
<th>Saturated fat (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example moderate to high-cholesterol foods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beef liver, pan-fried</td>
<td>85</td>
<td>3 oz</td>
<td>324</td>
<td>1.3</td>
</tr>
<tr>
<td>Egg, whole, raw, fresh</td>
<td>50</td>
<td>1 large</td>
<td>212</td>
<td>1.6</td>
</tr>
<tr>
<td>Shrimp, breaded and fried</td>
<td>164</td>
<td>6 – 8 shrimp</td>
<td>200</td>
<td>5.4</td>
</tr>
<tr>
<td>Chicken breast, meat and skin, battered, fried</td>
<td>140</td>
<td>½ breast</td>
<td>119</td>
<td>4.9</td>
</tr>
<tr>
<td>Pie, pecan</td>
<td>122</td>
<td>1 slice</td>
<td>106</td>
<td>4.9</td>
</tr>
<tr>
<td>Turkey, meat only, roasted</td>
<td>140</td>
<td>1 cup</td>
<td>106</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Example moderate to high-saturated fat foods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast food taco</td>
<td>263</td>
<td>1 large</td>
<td>87</td>
<td>17.5</td>
</tr>
<tr>
<td>Fast food biscuit with egg and sausage</td>
<td>180</td>
<td>1 sandwich</td>
<td>302</td>
<td>15.0</td>
</tr>
<tr>
<td>Milk shake, vanilla</td>
<td>333</td>
<td>16 fl oz</td>
<td>77</td>
<td>13.2</td>
</tr>
<tr>
<td>Hamburger, with condiments</td>
<td>218</td>
<td>1 sandwich</td>
<td>87</td>
<td>10.4</td>
</tr>
<tr>
<td>Candies, semisweet chocolate</td>
<td>42</td>
<td>¼ cup</td>
<td>0</td>
<td>7.5</td>
</tr>
<tr>
<td>Trail mix, tropical</td>
<td>70</td>
<td>½ cup</td>
<td>0</td>
<td>5.9</td>
</tr>
</tbody>
</table>

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3 An $r = 0.31$ means that the relationship reported by Hegsted accounts for only 9.6% ($r^2$) of the variability.
Bioavailability of dietary cholesterol

Absorption of ingested cholesterol is typically in the range of 40% to 60%, but can vary from 20% to 80% (Institute of Medicine, 2005a). Intestinal transit time, the amount of cholesterol in the diet, and genetic factors may contribute to this variability (Institute of Medicine, 2005a). Foods containing viscous fiber (e.g., oats, guar gum, pectin, psyllium) can interfere with the absorption of dietary fat and cholesterol, and impede the reabsorption of endogenous cholesterol and bile acids (Institute of Medicine, 2005b; Jenkins et al., 2003). High intake of plant sterols may also reduce cholesterol absorption (Institute of Medicine, 2005b).

Consumption data

Data for U.S. cholesterol consumption are available from analysis of USDA's Continuing Survey of Food Intakes by Individuals (CSFII), which measured foods eaten by representative individuals in the United States using 24-hour dietary recalls (Economic Research Service, 2004). Data taken in aggregate from this and other U.S. food surveys [i.e., NHANES, National Food Consumption Survey] indicate that daily cholesterol intake decreased from the 1970s to the 1990s (Cooper et al., 2000). Then, daily cholesterol consumption increased from 1996 to the year 2000 (Basiotis et al., 2006).

In general, there can be large day-to-day variation in cholesterol intake for any one individual and among individuals in the population (Hopkins, 1992). In the 1990s, the average daily cholesterol intake of children (ages 2 to 17) was 225 mg/d and that of adults 18 years of age and older was 271 mg/d (Economic Research Service & U.S. Department of Agriculture, 2006). Among adults ages 60 and older, women consumed less saturated fat and cholesterol than men: 17 g and 202 mg versus 24 g and 288 mg, respectively. These differences were due primarily to women consuming less energy (kcal/d) than men. Men and women in this older age group had similar averages for the cholesterol density of their diets (mg nutrient per 1000 kcal), consuming approximately 140 to 150 mg cholesterol per 1,000 kcal. This is higher than the cholesterol density of the diet of children (115 mg/1,000 kcal) and of all adults aged 18 and older (132 mg/1,000 kcal). At least 30% of men surveyed in 1994-1996 exceeded recommendations for daily cholesterol intake (Dixon & Ernst, 2001). Food survey data collected through 1998 indicated that two population groups, boys 12 to 19 years of age and men 20 years of age and older, are consuming, on average, more than 320 mg/d of cholesterol (Dixon & Ernst, 2001).

New nationwide dietary intake data for the years 2001-2002, What We Eat in America, are the result of integrating the dietary intake surveys CSFII and NHANES, conducted by the USDA and the U.S. Department of Health and Human Services, respectively. USDA (2006d) is planning to release summary data tables containing new estimates of usual cholesterol intake.

1.2.3 Dietary guidelines

As science has advanced and the associations between diet and health have become better understood, dietary guideline documents have become increasingly complex. Such documents can contain materials for the general public as well as scientific background information for health professionals. The Food and Agricultural Organization of the United Nations and the World Health Organization distinguish between two types of dietary recommendations, the technical documents that serve to inform health professionals and federal regulators, and the food-based dietary guidelines that serve to educate and guide the general public (Clay, 1997).
LSRO Report: Approach to Establish Guidelines for Cholesterol Intake

The latter comprise sets of advisory statements to promote overall nutritional well being, whereas the technical type of recommendations, such as Dietary Reference Intakes, are expressed as goals for intake of specific nutrients and food components. The technical documents often inform the development of the food-based population guidelines, but both types of recommendations should be based on sound scientific evidence (Clay, 1997).

In contrast to dietary guidelines for the general public, clinical treatment guidelines are recommendations that are designed to assist health practitioners and their patients in making appropriate health care decisions about a specific condition or treatment (Health Compass, 2006). Clinical guidelines are usually developed by a panel of experts under the auspices of a medical association or government agency and are based on a thorough review of scientific studies on the topic being addressed. Clinical recommendations for some food components may be the same as or similar to dietary guidelines for the general public. In this LSRO report, the general terms “recommendations” and “guidelines” are used interchangeably.

Overview of methods for guideline development

The development of dietary guidelines is complicated, time-consuming and expensive. Various methodologies are used to develop and update dietary guidelines, which rely to varying degrees on formal methods of analysis of scientific evidence and expert opinion. Common to all processes is the goal of reviewing up-to-date scientific data, and where possible, constructing feasible guidelines based on data rather than judgment. Differences in the review process and in the focus of the literature search can contribute to differences in the recommendations disseminated. Differences in the expert knowledge base of consensus committees could account for differences in their guideline recommendations, especially if different literature is reviewed, different assessments are made of similar literature, different mechanisms are used to make decisions, different outcome measures are examined, or competing interests bias the process (Cooper & Zlotkin, 2003).

In the late 1970s, the National Institutes of Health (NIH) introduced the consensus conference as the first formal method for guideline development to replace less rigorous informal consensus procedures (Roche & Durieux, 1994). These efforts underscored the need for a full complement of multidisciplinary experts, free from conflicts of interest, to oversee the collection, selection, review, and evaluation of scientific literature. NIH concluded that tools and techniques utilized in the search for literature are necessarily a major determinant of the quality of the publications collected for expert review. Also, without adequate control measures for relevancy, an enormous quantity of literature could easily be amassed. On the other hand, a too-stringent or overly narrow search might not capture important findings. Hence, NIH developed an appreciation for the judicious choice of key words and other search strategies to retrieve relevant materials from databases, and the need for competent researchers to fulfill this task. Also highlighted by this NIH consensus conference was the value of public participation to contribute extra data and other points of view for consideration that might not have been otherwise addressed by the conference experts.

Also arising out of public policy efforts to develop nutrition goals in the 1970s was the practice of categorizing the quality of scientific evidence (Ahrens, Jr., 1979). In this technique, study designs are rated during the literature review. For example, prospective, randomized controlled trials are assigned a higher rating than retrospective studies that lack an experimental diet or treatment. Some expert committees also assign letter grades to each of their recommendations to
indicate the strength of the scientific evidence upon which the recommendations were based. In this case, a grade of “A” would indicate there was strong evidence from several high-quality studies to support the recommendation. Such grading (particularly low grading) is useful to make clear the uncertainties that persist in the final document.

The dissemination of dietary guidelines is typically, but not always, accompanied by evidence tables and a description of the process leading to the recommendations. The extent to which the details of the process are disclosed and evidence is described varies widely in guideline documents.
II. UNITED STATES DIETARY RECOMMENDATIONS
   II.1 EARLY U.S. EFFORTS
      II.1.1 American Heart Association and Inter-Society Commission for Heart Disease Resources
      II.1.2 United States Senate Select Committee On Nutrition And Human Needs
      II.1.3 Surgeon General’s Report
   II.2 DIETARY REFERENCE INTAKES
      II.2.1 Overview
      II.2.2 Approach
      II.2.3 Effects of dietary cholesterol on coronary heart disease
      II.2.4 Effects of dietary cholesterol on blood lipoproteins
      II.2.5 Institute of Medicine recommendations
   II.3 DIETARY GUIDELINES FOR AMERICANS
      II.3.1 Twenty-six year history
      II.3.2 Revision process leading to 2005 guidelines
      II.3.3 Evidence report for dietary cholesterol guideline
      II.3.4 Guideline recommendations
   II.4 SUMMARY OF U.S. DIETARY RECOMMENDATIONS
II. UNITED STATES DIETARY RECOMMENDATIONS

In the United States, there are two complementary but separate federal efforts to review scientific evidence and translate this data into dietary recommendations. The U.S. Department of Agriculture (USDA) in collaboration with the U.S. Department of Health and Human Services (DHHS) periodically issues dietary guidelines for Americans. These guidelines are concise food-based recommendations written in lay language for use by the general public and pertain to individuals who are at least two years old. The recommendations are intended to promote healthy diets and reduce risk of major chronic diseases. Continuing development and revision of dietary guidelines relies on another federal effort, that of the Food and Nutrition Board of the Institute of Medicine (IOM), which reviews advances in science to update its Dietary Reference Intakes (DRI). In contrast to dietary guidelines, DRI are recommendations for specific nutrients and other components of food, written in scientific terms, for use by government regulators, health professionals, nutrition educators, and other stakeholders. For example, the DRI discussion of dietary cholesterol is considered when updating dietary guidelines.

U.S. law requires that expert advisory committee nominations, deliberations, and meetings be public and preceded by public notice, to ensure transparency and stakeholder involvement (Dwyer, 2006). Mandatory public comment periods permit stakeholders to submit their opinions for consideration before recommendations are finalized (Dwyer, 2006).

II.1 EARLY U.S. EFFORTS

In the 1950s and 1960s, awareness was growing that typical U.S. blood cholesterol concentrations were too high and that this abnormality was associated with a high frequency of morbidity and mortality caused by coronary heart disease (CHD). By 1957, the amount and types of fat consumed (i.e., saturated versus unsaturated) and excess energy consumption were suspected of altering blood lipids and health outcomes (Keys et al., 1957). Yet, there was concern that existing knowledge of nutrition was not sufficient to anticipate what results would occur if the public were encouraged to radically alter its basic dietary patterns (Pollack, 1957). In this atmosphere of cautious concern, the American Heart Association (AHA) recommended that the general population decrease total fat intake from the typical 40% to 45% of calories to 25% to 30% of calories (Page et al., 1957). Further clinical investigations using standardized methods for cholesterol analysis were encouraged to permit comparisons across studies (Dayton et al., 1965; Page et al., 1957). Concerns continued to mount as heart disease claimed large numbers of American lives. In 1964, U.S. men had the third-highest mortality rate for CHD among middle-aged men from 22 countries (Inter-Society Commission for Heart Disease Resources, 1970).

II.1.1 American Heart Association and Inter-Society Commission for Heart Disease Resources

Threshold for hypercholesterolemic patients – 1960s

In the early 1960s, the membership of the AHA Ad Hoc Committee on Dietary Fat and Atherosclerosis included Irvine Page (Chairman), Edgar Allen, Francis Chamberlain, Ancel Keys, Jeremiah Stamler, and Fredrick Stare. This distinguished group researched the associations of dietary fat, dietary cholesterol, blood cholesterol concentration, and development of atherosclerosis (Page et al., 1961). At that time, they understood the disease process to be
“much more complex” than simply suggesting that individuals eat less foods containing cholesterol. They recommended that men who are prone to cardiovascular disease because of family history, overweight, elevated blood cholesterol, high blood pressure, and/or who “lead sedentary lives of relentless frustration” should consider moderating total energy intake and decrease total fat intake to 25% to 35% of calories.

In 1965, the AHA Committee on Nutrition was asked by its advisors to prepare an up-to-date statement to inform the public on the relationship between diet and heart disease and to provide the best advice available. The committee was aware of the association between blood cholesterol and the incidence of CHD and supported an approach that reduced blood cholesterol by modifying diet as well as other risk factors. The public was advised to eat less animal (saturated) fat, eat less food rich in cholesterol, increase intake of unsaturated vegetable oils, and reduce caloric intake as needed to achieve and maintain a desirable body weight (American Heart Association Committee on Nutrition, 1965). The value of prevention was emphasized by encouraging these practices early in life and by making sound food habits a “family affair.”

In 1968, the Medical Boards of Norway, Sweden, and Finland released a collective recommendation for the general Scandinavian population, designed to help prevent CHD. These medical boards recommended that the amount of calories in the diet should, in many cases, be reduced to prevent overweight, that total fat should be between 25% and 35% of calories, that saturated fat intake should be reduced, that polyunsaturated fat intake should increase, and they encouraged consumption of fruits, vegetables, skim milk, lean meat, fish and cereal. In response, Keys (1968b) wrote an editorial addressing the importance of such authoritative recommendations and noted that counterparts in the United States (e.g., the Surgeon General’s Office of the U.S. Public Health Service) had not addressed CHD as specifically in their recommendations as did the Scandinavians but, instead, relied on individual physicians to recommend healthful diets to their patients. Later that year, Keys (1968a) reviewed the University of Iowa College of Medicine text A Low Cholesterol Diet Manual, which prescribed a plan for lowering dietary fat to 20% of energy and cholesterol to 100 mg in 2400 kcal (42 mg/1000 kcal). He noted, “Insistence on such severe dietary restrictions of cholesterol-containing foods gives too much credit to the effect of cholesterol in the diet.”

The AHA Committee on Nutrition (1968) revised its 1965 statement on the relationship between diet and heart disease to incorporate accumulated data on the effects of diet on myocardial infarction. The revised statement was designed primarily for the scientific community and was a summary of more detailed discussions (Page & Stamler, 1968b). At that time, AHA also produced several consumer-oriented booklets on related topics for the general public and for patients on prescribed fat-controlled and calorie-controlled diets (American Heart Association Committee on Nutrition, 1968).

The AHA Committee on Nutrition (1968) recognized that a fat-modified diet might minimize the progressive rise in blood cholesterol concentration that generally occurs in most adults, but noted that this preventive hypothesis had yet to be proven. Its recommendations were intended for “healthy” individuals, including those individuals with elevated blood lipids. The committee acknowledged that the optimal amount of fat was not known but suggested consuming less than 40% of calories from fat. The nutrition target was a diet moderate (not low) in total fat of 25% to 35% of calories, the same as the AHA 1961 recommendation (Page et al., 1961), but permitted up to 40% of calories from fat in the treatment of patients with hypertriglyceridemic hyperlipidemia. The treatment regimen for this subgroup of patients was to replace a portion of
carbohydrate with polyunsaturated vegetable oils, while the intake of saturated fat and cholesterol was kept low (Page & Stamler, 1968b).

The committee recommended that the general public substantially reduce cholesterol from the average daily intake of 600 mg/d. For hypercholesterolemic individuals, it further recommended a cut-off for dietary cholesterol of less than 300 mg/d (American Heart Association Committee on Nutrition, 1968; Page & Stamler, 1968b; Page & Stamler, 1968a). The committee also recommended that intake of vegetables, cereals, and fruit should serve as the primary source of dietary carbohydrate instead of sugar, particularly as candy, soft drinks, and other sweets. The committee also recommended adjusting caloric intake to achieve and maintain proper body weight because obesity was known to be associated with hypertension and diabetes, and was secondarily associated with CHD. Finally, the committee recommended that changes in diet must preserve the principles of good nutrition, especially for children and for women who are pregnant or lactating.

**Evidence-base for 1968 recommendations**

The AHA Committee on Nutrition (1968) acknowledged that much of the cholesterol data at that time was from adult men who were susceptible to CHD or otherwise atypical of the general U.S. population. Studies had shown that modified diets could reduce blood cholesterol in most (but not all) persons having elevated blood total cholesterol (Page & Stamler, 1968b). In supporting documents, Page & Stamler (1968b) referred to the experience of diet modification in the Chicago Coronary Prevention Evaluation Program (Stamler et al., 1968) and the Oslo Study (Leren, 1966), which supported restricting dietary cholesterol to 300 mg/d for hypercholesterolemic patients. Those experimental diets contained 307 ± 94 mg/d and 264 mg/d, respectively.

The Chicago Coronary Prevention Evaluation Program (Stamler et al., 1968) attempted to minimize five coronary risk factors: hypercholesterolemia, obesity, hypertension, cigarette smoking, and physical inactivity (Stamler et al., 1966). For the 335 hypercholesterolemic men enrolled in the study (baseline blood total cholesterol of 260 mg/dL or greater), the six-year drop-out rate was 33.7%. Participants in the intervention group (n=99 subsample) consumed an average of 30% of calories from total fat, 10% of total calories as saturated fat, and 307 ± 94 mg/d (184 mg/1000 kcal) of cholesterol compared to a matching cohort, who consumed an average of 43% of calories from total fat, 17% of total calories as saturated fat, and 627 ± 220 mg/d (254 mg/1000 kcal) of cholesterol. The intervention group (n=156 subsample) had an average 16.1% decline in blood total cholesterol. The authors attributed a wide range in serum responses to several factors: baseline concentration, adherence to diet, and individual inherent responsiveness (Stamler et al., 1968).

The Oslo Study (Leren, 1966) was a five-year clinical trial of male survivors of myocardial infarction, in which 84% of patients in the diet group (total n=206) were considered to have good or excellent adherence to the prescribed low fat diet based on questionnaires obtained six times during the study. The mean reduction in blood total cholesterol over five years for the diet group was 17.6% (52 mg/dL) compared to 3.7% (11 mg/dL) in the control group (n=206). For 17 patients having baseline average blood total cholesterol of 294 mg/d who were selected to represent “the especially conscientious and positive type” of participant, a greater average reduction in blood total cholesterol of 30% was achieved. For these patients, intake of cholesterol was 264 mg/d (111 mg/1000 kcal) and fat intake was 39% of total calories. Soybean
oil represented 72% of the total dietary fat and one egg with yolk was permitted each week. The incidence of myocardial reinfarction (i.e., both the total number of patients with reinfarction and the number with fatal infarctions) was greater in the control group. This difference did not become statistically significant until the third year of the trial. There was no difference in the incidence of sudden death between groups. However, for those patients younger than 60 years of age, the relapse rate for CHD (i.e., total numbers combined for myocardial reinfarction, new cases of angina pectoris, and sudden death) was statistically lower in the diet group. Leren (1966) indicated that the greatest beneficial effect of the cholesterol-lowering diet was evident in those persons who at the start of the trial had a normal diastolic blood pressure, a normal relative heart volume, and did not have angina pectoris.

Based on the report of Connor et al. (1964) and an advanced draft of the seventh edition of the Recommended Dietary Allowances (RDA), the AHA Committee on Nutrition recognized that a sharp decline in dietary cholesterol could lower blood total cholesterol concentrations in healthy individuals. The seventh edition of the RDA (National Research Council, 1968) refers to an early report by Connor et al. (1961a) in which six healthy male prisoners, three per group, were fed alternating high-cholesterol or cholesterol-free metabolic formula diets in a cross-over design. When consuming six or more egg yolks in the high-cholesterol diet, blood cholesterol increased whereas blood cholesterol decreased when fed a cholesterol-free diet. Similar results were published in a later study of three healthy male prison volunteers and three men with insulin-dependent diabetes (Connor et al., 1964). When intake was switched (from a diet containing 729 mg/d cholesterol, 16% total energy as saturated fat, and 4% total energy as polyunsaturated fat) to a diet with similar levels of fat but no cholesterol, mean blood total cholesterol decreased 18% \((P < 0.001)\) from 213 mg/dL to 175 mg/dL. Yet, when saturated fats and polyunsaturated fats were further reduced to 8% and 12% of total energy, respectively, no further significant reduction in blood cholesterol was observed. When 725 mg/d cholesterol was added back into the diet, mean blood total cholesterol rose significantly by 28 mg/dL \((P < 0.02)\).

The AHA Committee on Nutrition also referred to a cross-over trial, in which Turpeinen et al. (1968) enrolled 581 men in two mental hospitals in Finland over a six-year period. The diet period ranged from one month to six years, depending on the length of patient stay. In one hospital the regular house diet was maintained and served as the control diet. In the other hospital, whole milk, butter, and stick margarine were replaced by skim milk with added soybean oil and tub margarine. In the control facility, intake averaged 514 mg/d of cholesterol (178 mg/1000 kcal) and 34-37% of calories from fat. Men on the experimental diet averaged 228 mg/d of cholesterol (81 mg/1000 kcal) and 30-32% of calories from fat. Mean total blood cholesterol declined from 236 mg/dL at baseline to 215 mg/dL after six weeks and to 217 mg/dL after six years for the intervention facility. The difference in mean blood total cholesterol between the two facilities varied between 43 and 67 mg/dL after the diet change, the average difference of 51.3 mg/dL for men on the experimental diet was highly significant.

The AHA Committee on Nutrition (1968) and Page & Stamler (1968b) also cited the experience of diet modification in men considered to be in good health and free of CHD at the time of enrollment in the Diet and CHD Study Project, generally referred to as the Anti-Coronary Club (Christakis & Rinzler, 1969), in the Los Angeles Veterans Administration Domiciliary Study (Dayton et al., 1965), and in the National Diet-Heart Study (American Heart Association, 1968d). Intervention diets in these latter two studies contained 365 mg/d and 282-289 mg/d of cholesterol, respectively.
The Diet and CHD Study Project was pioneered by staff in the Department of Health of the City of New York (Christakis & Rinzler, 1969). Their objective was to determine whether a “prudent diet” capable of lowering blood cholesterol could favorably influence morbidity and mortality due to CHD. The rationale for diet modification was based on: (1) international epidemiological studies indicating statistical associations between diet, mean blood total cholesterol concentration in population groups, and the incidence of CHD; (2) the Framingham Study’s identification of risk factors of CHD, which included elevated blood total cholesterol; and (3) preliminary findings that dietary polyunsaturated fat might exert a depressant effect on blood cholesterol. Because the diet would be consumed for a prolonged period by a volunteer study population of middle-aged men, the investigators endeavored to make the test diet palatable, varied, and nutritious as well as cholesterol-lowering. The Anti-Coronary Club’s “prudent diet” did not specify an intake level for cholesterol but did restrict foods containing high amounts of cholesterol and/or saturated fat (e.g., eggs, butter, whole-milk cheeses, beef, pork, and lamb), and encouraged consumption of foods containing polyunsaturated fat.

In the course of nine years, the investigators of the Diet and CHD Study Project gained experience with 1,000 participants. They encountered difficulties with dietary compliance, primarily from restrictions on pastries, limitations on portion size and frequency of high-fat meats, the prohibition of ice cream, and the limited availability of diet-compliant foods in meals eaten away from home. The “prudent diet” lowered blood total cholesterol in 80% of participants having baseline concentration of 270 mg/dL or greater, in 60% of participants exhibiting baseline levels of 230 to 269 mg/dL, and in 30% of those whose baseline level was under 230 mg/dL (Christakis & Rinzler, 1969). For the 332 subjects remaining active in the experimental group and the 329 subjects in the control group still participating in the study after four years, risk factor status was compared at time of entry, after two years, and after four years of participation. The prevalence of hypercholesterolemia, obesity, and hypertension decreased substantially for the diet group after two years and remained depressed after four years. In contrast, little change in those risk factors was observed for the control group at these time periods. Among participants 40-59 years of age, there were 17 new confirmed coronary disease events in the active diet group (n=941) compared with 32 in the control group (n=457); the observed incidence rate of coronary disease events per 100,000 person-years of experience was 430 in the active diet group compared with 1025 in the control group.

The National Diet-Heart Study (American Heart Association, 1968c) was planned as a one- to two-year fat-modified diet for free-living and institutional populations to test the feasibility of conducting a larger, longer-term trial on a double-blind basis. Facilities for the study of free-living or “open” populations were established in five cities: Baltimore (n=234), Boston (n=225), Chicago (n=226), Minneapolis-St. Paul (n=225), Oakland (n=247), and in an institutional population at the Faribault State School and Hospital in Minnesota (n=166). Men in good health, ranging from 40 to 59 years of age, with blood total cholesterol less than 350 mg/dL were assigned to one of three protocol diets on a stratified random basis using blood cholesterol, systolic blood pressure, body weight, and cigarette smoking status (American Heart Association, 1968b). At each center, two groups of subjects were to consume 350-450 mg/d of cholesterol and a control group was to consume 650-750 mg/d. However, 28-week food records indicated that actual consumption averaged 282-289 mg/d in the intervention groups and 322 mg/d in the control groups. The intervention diets averaged 30%-34% of energy as total fat, 7% of energy as saturated fat, and either 10% or 13% of energy as polyunsaturated fat (American Heart Association, 1968c). The control diet averaged 35% of energy as total fat, 12% of energy as saturated fat, and 5% of energy as polyunsaturated fat. Two additional diets were tested with
other participants in Minneapolis and Faribault. Complete data were available for 921 men (612 on intervention diets and 309 on control diets). The average response in blood total cholesterol after 52 weeks on the two intervention diets was a decrease of 25.4 mg/dL (-10.8%) and 27.6 mg/dL (-11.7%) for participants in the “open” centers and a decrease of 36.2 mg/dL (-16.5%) and 31.3 mg/dL (-15.0%) for participants in the institutional setting. The greatest reductions in blood cholesterol concentrations tended to be in those individuals with higher baseline concentrations and those who lost the greatest amount of weight from the baseline period. In contrast, usual diets of 35% of energy as total fat, 12% of energy as saturated fat, and 322 mg/d of dietary cholesterol nearly maintained blood total cholesterol at mean baseline concentration of 230 ± 1.3 mg/dL at “open” centers and 207 ± 2.9 mg/dL at the institution. The average response on the control diet was a reduction in blood total cholesterol of 6.5 mg/dL (-2.4%) from baseline after 52 weeks for participants in the “open” centers, and a reduction of 3.9 mg/dL (-2.1%) for participants in the institution, measured from weeks 20 to 52 (the diet was adjusted at 12 weeks to raise blood cholesterol concentration closer to baseline values).

Threshold for the general public–1970’s and 1980’s

The efforts of AHA were extended by the Inter-Society Commission for Heart Disease Resources (the Commission), which was established in 1969 through a contract with AHA under Public Law 89-239. Before it disbanded, the Commission issued dietary recommendations for preventing or controlling hyperlipidemia, obesity, hypertension, and diabetes as one of several strategies aimed at primary prevention of premature atherosclerotic diseases (Dixon & Ernst, 2001; Inter-Society Commission for Heart Disease Resources, 1970; Kannel et al., 1984). The recommendations in its report, Primary Prevention of the Atherosclerotic Diseases, were based on encouraging findings reported by the New York Anti-Coronary Club, the Helsinki Mental Hospital Study, and the Los Angeles Veterans Administration Study. Although recognizing that CHD death rates were not significantly different between control and intervention diets, the Commission nevertheless concluded that these studies demonstrated a sizable decrease in the incidence of new coronary events after dietary saturated fat and cholesterol were reduced and polyunsaturated fat was added (Inter-Society Commission for Heart Disease Resources, 1970). The Commission recommended three main changes to the diet of the general public, particularly for individuals with marked increase in risk of premature atherosclerotic diseases:

- Adjust calorie intake to achieve and maintain optimal body weight
- Reduce dietary cholesterol to less than 300 mg/d (and avoid consumption of egg yolks)
- Substantially reduce dietary saturated fats to less than 10% of total calories

With regard to dietary cholesterol, there was no explanation for the Commission’s threshold of 300 mg/d other than an attempt to cut in half the estimated 600 mg/d average daily intake of the general population without overly impairing intake of protein. The rationale advanced by the Commission for promoting a reduction in dietary cholesterol was the evidence that intervention diets containing lower-than-typical amounts of saturated fat and cholesterol and increased amounts of polyunsaturated oils were able to reduce blood total cholesterol and decrease incidence of coronary events (Inter-Society Commission for Heart Disease Resources, 1970).

In conjunction with dietary recommendations for the general public, the commission also recommended that food manufacturers minimize egg yolk content of commercially prepared foods, that animals be bred and fed to yield leaner meats, that dairy and baked goods be produced with less saturated fat and cholesterol, and that use of polyunsaturated fats and oils be
promoted. It further recommended changing laws to permit use of vegetable oil in processed meat products (e.g., hot dogs, cold cuts); improve food labels to include cholesterol and the amount and type of other fat; and encourage policies, regulations, and practices of federal programs such as school lunch and food stamps to reduce consumption of saturated fat and cholesterol. Moreover, the commission suggested that large-scale, long-term clinical trials were necessary to determine the effects of such diet modifications on the rates of premature atherosclerotic diseases.

An updated statement for physicians and other health professionals on diet and CHD was prepared by the AHA Committee on Nutrition (1978). The following four recommendations were intended for the general population to lower blood lipids: adjust calories to achieve and maintain ideal body weight, decrease total fat intake to 30%-35% of energy (from an estimated 40% in the U.S. diet), decrease saturated fat to less than 10% of energy, and decrease cholesterol intake to less than 300 mg/d, with a caution to assure adequate protein intake if stringent restriction of cholesterol is undertaken, as might be warranted for persons with severe hypercholesterolemia. As references for its recommendations, the committee cited the National Heart Diet Study (American Heart Association, 1968c), an editorial by Stolley (1972) supporting the report Primary Prevention of the Atherosclerotic Diseases (Inter-Society Commission for Heart Disease Resources, 1970), and a statement by the American Medical Association Council on Foods and Nutrition (1972) that encouraged routine measurement of blood cholesterol and appropriate dietary advice for persons in risk categories, assigned on the basis of their blood lipid levels. Neither of the latter two publications directly addressed a threshold value for dietary cholesterol intake. As noted earlier, the National Heart Diet Study demonstrated an 11% reduction in blood total cholesterol in those consuming diets averaging less than 35% of kcal as total fat, 7% of kcal as saturated fat, and less than 300 mg/d of cholesterol, whereas those consuming higher amounts of fat and cholesterol experienced less than a 3% change in blood total cholesterol (American Heart Association, 1968a).

In 1983, the AHA Task Force Committee of the Nutrition Committee and the AHA Cardiovascular Disease in the Young Council offered the recommendation that daily cholesterol intake by healthy children over the age of two years should be approximately 100 mg/1000 kcal, not to exceed 300 mg/d (Weidman et al., 1983). The president of AHA at that time, Dr. Antonio Gotto, explained that limiting dietary cholesterol was prudent because it may lessen the risk for CHD and no harm could be foreseen. The rationale for the specific recommended intake of cholesterol by children was not reported. The Committee on Nutrition of the American Academy of Pediatrics urged that current dietary trends in the United States to decrease consumption of saturated fat, cholesterol, and salt, and increase intake of polyunsaturated fat should be followed in moderation. Diets that avoid extremes are safe for children for whom there is no evidence of special vulnerability (American Academy of Pediatrics, 1983; 1986).

The Inter-Society Commission for Heart Disease Resources report (1970) was revised in 1984 by the Atherosclerosis Study Group (Kannel et al., 1984). Then, as now, the primary goal of recommending a low-fat diet was to decrease blood low density lipoprotein (LDL)-cholesterol. This group’s review of international epidemiological evidence led to its inferring that there is a positive relationship between dietary fat (total and saturated), dietary cholesterol, and mortality from CHD (Kannel et al., 1984). It further concluded that “strong evidence exists that reducing dietary saturated fat and cholesterol can lower serum cholesterol to a range corresponding to a substantially lower risk.” Evidence of the specific contribution to outcome derived from reducing dietary cholesterol was not reported.
Citing McGandy & Hegsted (1975) and Keys et al. (1965a), the Atherosclerosis Study Group reported (on page 167A) that “100 mg of dietary cholesterol (per 1000 kcal) causes a 5 mg% increase in serum cholesterol.” However, it appears the Atherosclerosis Study Group (Kannel et al., 1984) may have confused units when it cited McGandy & Hegsted (1975). The review by McGandy & Hegsted primarily focused on results of Hegsted et al. (1965) and later studies that supported an increase in blood total cholesterol of approximately 5 mg/dL per 100 mg/d of added dietary cholesterol.

Hegsted et al. (1965) fed diets containing 38% of calories as fat to patients in a mental institution, most of whom were schizophrenic, and all of whom had baseline blood total cholesterol in the range of 200 to 300 mg/dL. Test diets lasting four weeks were fed to groups of 9 to 11 patients, and then alternated with control diets of the same duration. The source of added fat was coconut oil, olive oil, or safflower oil. Energy was supplied at 2200, 2600, or 3000 kcal/d to maintain body weight. Cholesterol determinations by direct analysis of weekly composites of the 2600 kcal test diet indicated cholesterol content of 306 mg/d whereas a value of 555 mg/d was calculated based on published data. The dietary cholesterol in meat, eggs, and dairy foods contributed from 116 to 686 mg/d in the various diets, based on analyzed values. The blood response was similar for the three types of added-oil diets, an average increase of approximately 5 mg/dL per 100 mg/d of added dietary cholesterol. For example, for a 2600 kcal diet, a 100 mg/d increase in dietary cholesterol, from 300 to 400 mg/d (an increase of 38.5 mg/1000 kcal), would be expected to increase blood total cholesterol approximately 5 mg/dL. The multiple regression coefficient for dietary cholesterol derived by Hegsted et al. (1965) from intercorrelated data of fats and cholesterol indicated an increase in blood total cholesterol of 6.5 mg/dL per 100 mg/d of dietary cholesterol consumed; the standard deviation from the regression line was 12 mg/dL. The coefficient for dietary cholesterol varied somewhat depending upon the other variables included in the regression. Hegsted et al. (1965) cautioned that “equations of this kind are of little value in predicting what may happen to the serum cholesterol of an individual.”

McGandy & Hegsted (1975) also noted findings by Mattson et al. (1972) who fed 70 healthy male prisoners, aged 21 to 48 years, a cholesterol-free diet for 21 days. Subjects were then assigned to groups to either continue the cholesterol-free diet or were fed formulas to achieve cholesterol intakes of 106, 212, or 317 mg/1000 kcal. Mattson et al. (1972) concluded that “Each 100 mg cholesterol in 1000 kcal of diet resulted in approximately a 12 mg/100-mL increase in serum cholesterol.” For example, for a 2600 kcal diet, a 100 mg/1000 kcal increase in dietary cholesterol from 106 to 206 mg/1000 kcal (an increase of 260 mg/d, i.e., from 275.6 to 535.6 mg/d), would be expected to increase blood cholesterol approximately 12 mg/dL or approximately 4.6 mg/dL for each 100 mg/d of cholesterol added, similar to the findings of Hegsted et al. (1965).

As noted above, the Atherosclerosis Study Group (Kannel et al., 1984) also cited Keys et al. (1965a) to support its conclusion about the relationship of dietary cholesterol and blood cholesterol. Keys et al. (1965a) and Grande et al. (1965) reported a series of metabolic studies with 22 schizophrenic male patients fed controlled diets varying in cholesterol from 50 to 1550 mg/d for three weeks duration. Keys et al. (1965a) analyzed data from these experiments along with data from four other published studies (Beveridge et al., 1960; Connor et al., 1964; Erickson et al., 1964; Steiner et al., 1962) after mathematical corrections of blood total

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45 mg/dL. On page 170A, they rephrased this as “The average serum cholesterol can be expected to fall 5 mg/dL for each 100 mg decrease in intake,” which the reader might assume was per day or per 1000 kcal.

512 mg/100-mL = 12 mg/dL.
cholesterol were made for studies of short duration by assuming that 70% of the ultimate effect of the diet was achieved within eight days (Beveridge et al., 1960), and to adjust for diets differing in fatty acid composition (Connor et al., 1964). Keys et al. (1965a) calculated the average blood total cholesterol response to changes in dietary cholesterol as:

\[ \Delta \text{blood total cholesterol (in mg/dL)} = 1.5(Z_2 - Z_1) \]

where \( Z \) is the square-root of dietary cholesterol (mg/1000 kcal) and subscripts refer to the two different diets. Using this equation, Keys et al. (1965a) estimated the effect of a reduction of dietary cholesterol of 70 mg/1000 kcal, from 254 mg/1000 kcal to 184 mg/1000 kcal, as 1.5 \times (13.6 minus 15.9) or a 3.4 mg/dL drop in blood total cholesterol.

The Atherosclerosis Study Group (Kannel et al., 1984) noted that U.S. men were consuming approximately 400 mg/d of cholesterol, or 160 mg/1000 kcal (assuming an energy intake of 2500 kcal). Thus, using the Keys et al. (1965a) equation, a reduction in dietary cholesterol of 100 mg/1000 kcal (from 160 mg/1000 kcal to 60 mg/1000 kcal), a reduction of 250 mg/d, is estimated to decrease blood total cholesterol by 7.3 mg/dL \([i.e., 1.5 \times (7.74 \text{ minus } 12.6)]\). This is higher than the 5 mg/dL estimated by the Atherosclerosis Study Group for a reduction of 100 mg/1000 kcal.

In the face of high incidence of CHD, the Atherosclerosis Study Group considered going ahead with dietary recommendations for the general public rather than waiting for proof of efficacy, in part because it acknowledged that unifactor diet-heart studies were not feasible (Kannel et al., 1984). Assuming that the average blood total cholesterol could be expected to fall 5 mg/dL for each 100 mg \((\text{per } 1000 \text{ kcal})\) decrease in cholesterol intake, the Atherosclerosis Study Group recommended that dietary cholesterol should be reduced from the then-current 400 mg/d intake for men to less than 250 mg/d, an even greater reduction from the 300 mg/d maximum advocated earlier (Inter-Society Commission for Heart Disease Resources, 1970). Following from these assumptions, an individual who was consuming the typical amount of cholesterol and 2,500 calories, and who then reduced cholesterol intake to 250 mg/d (from 160 to 100 mg/1000 kcal), a decrease of 150 mg/d, would be expected to achieve a reduction in blood total cholesterol of 3.9 mg/dL \([i.e., 1.5 \times (12.6 \text{ minus } 10)]\) for the change in dietary cholesterol, and at most, a total reduction in blood lipids of 15-20% from all dietary modifications \(\text{(e.g., saturated fat, fiber)}\) combined. The rationale for selecting the specific threshold of 250 mg was not discussed in the report (Kannel et al., 1984). The Atherosclerosis Study Group assumed that dietary factors that raise or lower blood total cholesterol affect LDL-cholesterol in like fashion.

**Recent recommendations of the American Heart Association**

AHA guidelines have continued to reiterate the established population-wide threshold for cholesterol intake (Krauss et al., 2000): “although there is no precise basis for selecting a target level for dietary cholesterol intake for all individuals, AHA recommends less than 300 mg/d on average.” The selection of the cut-off value of 300 mg was still not discussed or referenced in the guideline document. Also, further reduction of dietary cholesterol to less than 200 mg/d was recommended for individuals with elevated LDL-cholesterol levels, diabetes, or cardiovascular disease. AHA advocated limiting foods high in saturated fat, *trans* fat, and/or cholesterol, such as whole milk products, fatty meats, tropical oils, partially hydrogenated vegetable oils, and egg yolks.

26
AHA recently released new diet and lifestyle recommendations to promote heart health for Americans over the age of two years (Lichtenstein et al., 2006). These replace the 2000 AHA guidelines. Recommendations were included to balance caloric intake and physical activity to achieve and maintain a healthy body weight, limit intake of saturated fat to less than 7% of energy, limit trans fat to less than 1% of energy, and limit dietary cholesterol to less than 300 mg/d. To achieve these goals, it was suggested that individuals select lean meats and vegetable alternatives to meat; select fat-free (skim) or low-fat (1% fat) dairy products; minimize intake of beverages and foods with added sugars and foods with hydrogenated fats; choose and prepare foods with little or no salt; and if alcohol is consumed, to do so in moderation. AHA further recommended that these guidelines be applied to meals prepared both at home and outside the home (Lichtenstein et al., 2006). No specific recommendations were made for egg consumption. For certain patients at higher risk, AHA stated that the recommendations may have to be intensified, but gave no further instruction.

AHA suggested that the strongest dietary determinants of elevated blood LDL-cholesterol are dietary saturated fat and trans fat intakes. It cited the National Cholesterol Education Program (NCEP) (Expert Panel on Detection Evaluation and Treatment of High blood Cholesterol in Adults, 2001) in support of its assessment that dietary cholesterol and excess body weight are also positively related to levels of LDL-cholesterol, but to a lesser extent. (See Appendix B.) As in earlier AHA documents containing dietary recommendations, the selection of the 300 mg/d cut-off for cholesterol intake was not discussed (Lichtenstein et al., 2006). It appears that AHA’s approach was to be consistent where possible with the Nutrition Facts panel on food labels and to uphold its 2000 recommendations for cholesterol intake unless new evidence suggested that a change would be prudent (Lichtenstein et al., 2006).

AHA’s most recent dietary recommendations for children and adolescents do not specifically set a quantitative ceiling for cholesterol intake but its food-based strategies of substituting vegetable oils for butter and animal fat and encouraging use of low-fat/skim milk and lean meats should generally limit dietary cholesterol (Gidding et al., 2006). The authors state that their recommendations “echo other recent public health dietary guidelines in emphasizing low intakes of saturated and trans fat, cholesterol, and added sugar and salt.” They refer practitioners to the Dietary Guidelines for Americans (U.S. Department of Health and Human Services & U.S. Department of Agriculture, 2005) and the Pediatrician Nutrition Handbook (American Academy of Pediatrics, 2004).

II.1.2 U.S. Senate Select Committee on Nutrition and Human Needs

The U.S. Senate Select Committee on Nutrition and Human Needs (the Select Committee), established in 1968, undertook an examination of the problem of escalating medical care cost (U.S. Department of Health and Human Services, 1988b). It concluded that improved nutrition was a key component of preventative medicine and was necessary for minimizing the growing costs of medical care (U.S. Senate Select Committee on Nutrition and Human Needs, 1977). The Select Committee aimed to improve public health by directly informing the public about healthy diets and by raising awareness of risk factors for chronic disease, particularly with regard to controllable dietary risk factors. The report Dietary Goals for the United States was intended to complement and extend the RDA, in part by providing further guidance on intake of macronutrients, cholesterol and sodium (U.S. Senate Select Committee on Nutrition and Human Needs, 1977). The purpose of this report was also to expand the nutrition targets of federal regulators and public health professionals, at that time most concerned with preventing hunger...
and nutrient deficiencies, by increasing awareness that over-consumption of certain foods/food components is associated with chronic diseases (Davis & Saltos, 1999).

Dr. Antonio Gotto, then chair of the Department of Medicine at Baylor, discussed the relationship between blood cholesterol and risk of heart disease before the Select Committee. The Select Committee recognized that the average American, at that time, consumed 600 mg/d of cholesterol, perhaps an overestimate given problems with analysis and lack of standardized reference materials. In setting Goal 6, “reduce cholesterol consumption to about 300 grams (sic) a day,” the Select Committee (1977) intended for the dietary goal to be achieved as an average over several days, and that the goal value was the center of a range (250 to 350 mg) of recommended intake [see page xxvi of the report (U.S. Senate Select Committee on Nutrition and Human Needs, 1977)]. The Select Committee suggested that its recommendations reiterated the recommendations of professional and governmental bodies in the United States and other countries (Tables II-1 and II-2).

Diets developed using the Select Committee recommendations to trim fat from meats and substitute more vegetable protein for meat protein differed markedly from usual food patterns of that time (Davis & Saltos, 1999). In November 1977, the Select Committee released Dietary Goals for the United States–Supplemental Views in an effort to address disagreement and controversy in feedback from the meat and egg industries, academia, health care organizations, and consumers. This was followed by a second full edition of the report in December 1977, which included two new sections, one on calorie control and one on alcohol consumption (U.S. Senate Select Committee on Nutrition and Human Needs, 1977).

In the supplemental forward of the second edition, Senators Percy, Schweiker, and Zorinsky noted the extreme diversity of opinions among nutrition scientists and other health professionals responding to the Select Committee’s dietary goals. The Senators addressed three main points: (1) whether advocating a specific restriction of dietary cholesterol to the general public was warranted at that time; (2) whether there are demonstrable benefits to individuals and the general public, especially with regard to CHD, from implementing the dietary practices recommended in the report; and (3) whether some of the goals and recommendations might be inaccurate given the inadequacy of current food intake data. They provided the following representative examples of the cholesterol controversy (U.S. Senate Select Committee on Nutrition and Human Needs, 1977):

On the question of whether or not a restriction of dietary cholesterol intake for the general public is a wise thing to recommend at this time, the Inter-Society Commission for Heart Disease Resources (1972), the American Heart Association (1973), and several other expert panels suggest a reduction of dietary cholesterol to less than 300 mg/d. Yet, in October 1977 the Canadian Department of National Health and Welfare reversed its earlier position and concluded in a National Dietary Position that: Evidence is mounting that dietary cholesterol may not be important to the great majority of people... Thus, a diet restricted in cholesterol would not be necessary for the general population. A similar conclusion was drawn in 1974 by the Committee on Medical Aspects of Food in its report to Great Britain’s Department of Health and Social Security. Between these points of view are groups such as the New Zealand Heart Foundation which recommends a range of daily cholesterol intake, the maximum of which roughly equals the current average American intake. Because of these divergent viewpoints, it is clear that science has not progressed to the point where we can recommend to the general public that
cholesterol intake be limited to a specific amount. The variances between different individuals are simply too great.

Similarly, the Senators provided examples of the same polarity of scientific opinion on the question of whether dietary change could reduce the rate of CHD. Some prominent scientists and physicians advocated that recommendations were premature and, hence, unwise whereas other leading scientists and physicians suggested CHD mortality can “probably be prevented annually through dietary change.” Because of the lack of agreement among scientists on the efficacy of dietary change, these Senators thought the American public would be in a better position to exercise freedom of choice if the following were stated in bold print with the dietary goals: “The value of dietary change remains controversial and science cannot at this time insure that an altered diet will provide improved protection from certain killer diseases such as heart disease and cancer.”

The Select Committee viewed the process of setting dietary goals as on-going, and anticipated that the nutrition community would take over responsibility for future editions of guideline documents (U.S. Senate Select Committee on Nutrition and Human Needs, 1977).

Table II-1. General Population—Early recommendations of 12 expert committees on dietary cholesterol and coronary heart disease

<table>
<thead>
<tr>
<th>Country</th>
<th>Daily dietary cholesterol (milligrams)</th>
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</thead>
<tbody>
<tr>
<td>United States:</td>
<td></td>
</tr>
<tr>
<td>Inter-Society Commission for Heart Disease Resources (1970)</td>
<td>&lt;300</td>
</tr>
<tr>
<td>American Health Foundation (1972)</td>
<td>300</td>
</tr>
<tr>
<td>American Heart Association (1973)</td>
<td>300</td>
</tr>
<tr>
<td>White House Conference (1973)</td>
<td>300</td>
</tr>
<tr>
<td>Norway, Sweden, and Finland (1968)</td>
<td>—</td>
</tr>
<tr>
<td>United Kingdom:</td>
<td></td>
</tr>
<tr>
<td>Department of Health and Social Services COMA* Report (1974)</td>
<td>—</td>
</tr>
<tr>
<td>Royal College Physicians &amp; British Cardiac Society (1975)</td>
<td>Reduce</td>
</tr>
<tr>
<td>New Zealand:</td>
<td></td>
</tr>
<tr>
<td>Heart Foundation (1971)</td>
<td>300–600</td>
</tr>
<tr>
<td>Royal Society (1971)</td>
<td>Reduce</td>
</tr>
<tr>
<td>Australia:</td>
<td></td>
</tr>
<tr>
<td>Academy of Science (1975)</td>
<td>&lt;350</td>
</tr>
<tr>
<td>Germany (Federal Republic) (1975)</td>
<td>300</td>
</tr>
<tr>
<td>The Netherlands (1973)</td>
<td>250–300</td>
</tr>
</tbody>
</table>

Abstracted from Appendix B of the report by the U.S. Senate Select Committee on Nutrition and Human Needs (1977).

*COMA: Committee on Medical Aspects of Food Policy.
Table II-2. High Risk Population—Early recommendations of 6 expert committees on dietary cholesterol and coronary heart disease

<table>
<thead>
<tr>
<th>Country</th>
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</thead>
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<td>United States:</td>
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<td>Heart Foundation (1971)</td>
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<td>Royal Society (1971)</td>
<td>Reduce</td>
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<td>Australia:</td>
<td></td>
</tr>
<tr>
<td>National Heart Foundation (1974)</td>
<td>&lt;300</td>
</tr>
<tr>
<td>International Society of Cardiology (1973)</td>
<td>&lt;300</td>
</tr>
</tbody>
</table>

Abstracted from Appendix B of the report by the U.S. Senate Select Committee on Nutrition and Human Needs (1977).

II.1.3 Surgeon General’s Reports

The mixed response to recommendations issued during the 1970s [e.g., Ahrens (1979)] raised awareness among health professionals and those in the food industry of the lack of consensus regarding the influence of certain food components on risk of chronic disease (McMurry, 2003). The release of Healthy People: The Surgeon General’s Report on Health Promotion and Disease Prevention in 1979 supported the growing acceptance by many in the health community that diet was linked to adverse health outcomes other than just nutrient deficiencies (U.S. Department of Health, 1979). This report, prepared by the U.S. Department of Health, Education, and Welfare, relied on papers from the 1978 Departmental Task Force on Disease Prevention and Health Promotion, as well as from other working groups sponsored by the U.S. Public Health Service, and from IOM. The organizations and individuals contributing information were acknowledged but most reference materials were not cited. The Surgeon General proposed that the health of U.S. citizens could be improved predominantly by preventative measures rather than by treatment of disease. He reported that deaths due to heart disease decreased 22% in the United States between 1968 and 1977, attributing this (and other health improvements) to nutrition, personal lifestyle changes, and other preventative factors. The Surgeon General further aimed to improve the health of adults and, by 1990, to reduce the mortality rate of those 25 to 64 years of age to fewer than 400 in 100,000. His primary objectives for accomplishing this goal were to reduce heart attacks, strokes, and deaths from cancer through better detection and control of high blood pressure, smoking cessation, exercise and fitness activities, prudent diet, and better stress management. He pointed to the preliminary results of a massive public health campaign in North Karelia, Finland, in which reductions in smoking, better blood pressure control, and lower-fat diets led to reduced incidence of heart attack and stroke. He concluded that Americans would probably be healthier, as a whole, if they consumed less fat. Hence, he recommended that individuals should adopt prudent dietary habits, consuming less saturated fat and cholesterol. He went on to state that training in nutrition for physicians and other health professionals should have high priority, and nutrition training and services should be promoted in hospitals and clinics.

Nearly a decade later, the Surgeon General reviewed the animal, epidemiologic, and clinical evidence of the relationship of diet and CHD in The Surgeon General’s Report on Nutrition and Health (U.S. Department of Health and Human Services, 1988a), prepared primarily for policy
makers. The Surgeon General concluded that humans are generally less sensitive to dietary cholesterol than most animal species, and among individuals, some are more sensitive and others more resistant to its effects. In his review of epidemiological data, he noted that a limited number of studies, such as the Western Electric Study (Shekelle et al., 1981), had shown diet (particularly the amount and type of fat in the diet) to affect the level of blood total cholesterol, whereas other studies failed to find any association of diet with blood cholesterol or CHD. Based on published equations for predicting change in blood total cholesterol from changes in the diet, the Surgeon General estimated that if a person consuming 2000 calories per day were to increase dietary cholesterol from 300 mg/d to 500 mg/d, blood total cholesterol would rise by 10 mg/dL. The Surgeon General noted inconsistencies across clinical studies in responses to diet and considered baseline blood cholesterol, composition and form of food, age, metabolic status, and duration of the experiment as potential factors contributing to these differences. Nevertheless, he considered that in general, interventions to lower elevated blood cholesterol had been shown in both animal and human studies to reduce CHD risk and to slow lesion progression. He concluded that the effect of dietary cholesterol on blood cholesterol was somewhat weaker and more variable among individuals than that of saturated fat. Before making recommendations, the Surgeon General (U.S. Department of Health and Human Services, 1988a) considered the deliberations and recommendations of the consensus conference Lowering Blood Cholesterol to Prevent Heart Disease, which was convened by the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute and the Office of Medical Applications; and he considered consensus recommendations by other expert groups. The NIH consensus conference panel asserted that average blood cholesterol levels in the United States were too high, largely because of high intakes of calories, saturated fat, and cholesterol. The NIH consensus conference panel recommended that all Americans older than two years of age limit daily cholesterol intake to 250 to 300 mg or less.

After reviewing the evidence and consensus documents, the Surgeon General recommended that the general public reduce its intake of total fat from the average at that time of 37% of energy and decrease intake of saturated fat from the level at that time of about 13% of energy (U.S. Department of Health and Human Services, 1988a). The Surgeon General recommended reducing the amount of cholesterol consumed below the then-average of 305 mg/d for women and 440 mg/d for men. The Surgeon General also suggested that two groups of adults would benefit from beginning a program of supervised dietary treatment: (1) those having blood total cholesterol of 240 mg/dL or higher, and (2) those with CHD or two or more risk factors for CHD and having blood total cholesterol of 200 to 239 mg/dL. Citing current NCEP guidelines at that time, he recommended that these individuals restrict dietary cholesterol to 300 mg/d and if, after three months, the response is insufficient, to further restrict intake to less than 200 mg/d.

II.2 DIETARY REFERENCE INTAKES

II.2.1 Overview

The Food and Nutrition Board of the IOM, working in cooperation with Canadian scientists, publishes a set of reference values for nutrient intakes that are periodically updated. The breadth and depth of this effort is reflected by the varied sources of funding, which include the Centers for Disease Control and Prevention, the Department of Defense, the DHHS Office of Disease Prevention and Health Promotion, Health Canada, NIH, USDA, the U.S. Food and Drug Administration (FDA), a private foundation fund, and a fund of corporate donors. Contributors
to the private and corporate funds include the Dannon Institute, M&M Mars, the Mead Johnson Nutrition Group, and Roche Vitamins (Institute of Medicine, 2005b).

The Committee on Food and Nutrition of the National Research Council was established in 1940 to advise the Army on nutrition problems related to national defense (National Research Council Committee on Food and Nutrition, 1941). At that time, there was a need for a reference of dietary essentials for the production of nutritious food that could support the health of military personnel (and the civilian population, should rationing be imposed) and for food relief efforts overseas during World War II. A five-page 1941 document entitled Recommended Dietary Allowances—A Yardstick for Good Nutrition, contained the first table in a series of reference values which listed recommended intake for energy and nine nutrients; and it also contained the chart Dietary Pattern to Meet the Recommended Allowances (National Research Council Committee on Food and Nutrition, 1941). Its authors reviewed literature and considered commentary from more than 50 nutrition authorities (Roberts, 1958). The initial values were revised in the 1943 publication Recommended Dietary Allowances (Reprint and Circular series No. 115) and have been expanded and updated periodically as nutrition science and food analysis techniques have improved. The RDA values serve as a reference for average daily nutrient intakes that are judged to maintain good nutrition status of most healthy individuals in the United States. The seventh edition, published in 1968, became the basis for what the FDA established as guidelines for the nutrition labeling of foods (i.e., U.S. Recommended Daily Allowances) (National Research Council, 1989b). Because cholesterol intake is not essential, there has not been an RDA for it. However, the 10th edition of the RDA (National Research Council, 1989b) did report the recommendation of the Food and Nutrition Board Committee on Diet and Health that dietary cholesterol should be less than 300 mg/d (Appendix C) (National Research Council, 1989a).

In the 1990s, the effort to publish DRI represented a major expansion of the RDA. The DRI Committee considered nutrient levels that might reduce the risk of chronic degenerative diseases. It defined upper limits of nutrient tolerance and also recognized non-essential food components that might have beneficial health effects (Institute of Medicine, 2005b). In 1995, the Food and Nutrition Board collaborated with the government of Canada to further harmonize nutrient reference intakes for North America. Because DRI activities are ongoing and iterative, reference values continue to be periodically reassessed and revised. The most recent DRI committee expressed its hope that representatives from Mexico will join in future DRI deliberations.

**II.2.2 Approach**

The current DRI recommendation for cholesterol was a product of the combined efforts of the DRI Committee, the Panel on DRI for Macronutrients (Macronutrient Panel), the Subcommittee on Upper Reference Levels of Nutrients (UL Subcommittee), and the Subcommittee on Interpretation and Uses of DRI (Institute of Medicine, 2005b).

The Macronutrient Panel of 21 international experts was assigned by the DRI Committee to review the scientific literature on dietary cholesterol and determine whether cholesterol intake influences health, whether food components alter cholesterol’s bioavailability, and to determine estimates of dietary intake that are compatible with good nutrition throughout the lifespan and that may decrease risk of chronic disease. It was further instructed to propose Tolerable Upper Intake Levels where scientific data of population subgroups are available and to suggest needed research to improve knowledge of the role of dietary cholesterol in health. (The Tolerable Upper
Intake Level is the highest average daily intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population.)

The UL Subcommittee assisted the Macronutrient Panel in applying a risk assessment model to cholesterol (Institute of Medicine, 2005b). There are four components to the model. First, the hazard is identified by determining whether any serious health risks are related to high cholesterol intake. Next, a dose-response assessment is conducted by selecting a critical dataset, identifying a no-observed-adverse-effect level or lowest-observed-adverse-effect level, deriving a Tolerable Upper Intake Level, and reporting the scientific uncertainty of this derivation. In general, derivation of a Tolerable Upper Intake Level accounts for normal variability in sensitivity, excluding subpopulations with extreme and distinct vulnerabilities such as those needing medical supervision. The third component of the model is an intake assessment in which the range and distribution of human intake of cholesterol is determined. This includes collecting information on the cholesterol intake of the general population, comparing the range of intakes among groups of individuals, and reporting the uncertainty of the intake estimate. Lastly, the risk is characterized by estimating the fraction of the population with consistent intakes above the Tolerable Upper Intake Level and determining the extent to which adverse health effects are reversible when cholesterol intake is reduced. This information would support formulation of a policy decision on whether efforts should be made to decrease risk for any disease that may be caused by chronically high cholesterol intake.

Similar to past DRI efforts, the Macronutrient Panel and collaborating DRI committees sought the advice of numerous outside experts. They held meetings to understand the importance of new data on the risks and benefits of food components and to resolve difficult issues. They also considered the critiques of independent reviewers. Many important questions that could not be satisfactorily answered were structured into recommendations for a research agenda.

**Types of evidence reviewed**

IOM reviewed three datasets regarding the association of dietary cholesterol and cardiovascular disease: preclinical animal models, epidemiological studies, and the effects of dietary cholesterol on blood lipoproteins in human clinical trials. Although IOM (2005a) recognized that experimental data in several animal species including transgenic mice, rabbits, pigs, and nonhuman primates provided evidence that dietary cholesterol can induce atherosclerosis, it decided that marked differences in cholesterol metabolism between species negated their extrapolation of data directly to humans. Hence, preclinical animal models were generally supportive but did not define IOM recommendations.

**II.2.3 Effects of dietary cholesterol on coronary heart disease**

IOM (2005a) reviewed 15 reports published from 1984 to 1999 about the effects of dietary cholesterol on heart disease. Among these, two studies by Hu *et al.* (1997; 1999) and two by McGee *et al.* (1984; 1985) used the same subjects and data in both their publications. Also, Ascherio *et al.* (1996) and Hu *et al.* (1999) used the same database of intakes and health outcomes in male health professionals.

Six of the 15 reports reviewed by IOM indicated a positive relationship between cholesterol intake and cardiovascular disease and/or CHD biomarkers (such as carotid artery wall thickness). Two of these six positive reports used the same database of intake data and outcomes McGee *et al.* (1984; 1985).
As indicated in Table II-3, cases of CHD were generally observed at moderate to high cholesterol intakes (mean intake > 250 mg/1000 kcal). One intervention study among cardiac patients did demonstrate the ability to reduce cholesterol intake significantly ($P < 0.03$) with nutrition education compared to usual care [$i.e., 215 \pm 15 \text{ mg/d (105 mg/1000 kcal)}$ compared to $341 \pm 23 \text{ mg/d (157 mg/1000 kcal), respectively}$] (Watts et al., 1994). However, the magnitude of the blood cholesterol response was not associated with the daily amount of dietary cholesterol during the study period (Table II-3).

Little evidence was discussed that supported a role for low levels of cholesterol intake in the primary prevention of CHD. In one paper cited by IOM, Mann et al. (1997) prospectively observed U.K. subjects ($n=9,980$) who were healthy at baseline for 13 years (Table II-3). They found a significant trend for increased death from ischemic heart disease from the 1st to 3rd tertile of cholesterol intake (less than 200 mg/d to more than 300 mg/d), yet there was a significant decrease in all cause mortality from the 1st to 2nd tertile of cholesterol intake, from less than 200 mg/d to 200-300 mg/d, as adjusted for age, sex, smoking, and social class.
Table II-3. Six studies cited by Institute of Medicine (2005a) as supporting a positive association between dietary cholesterol and CHD.\(^a\)

<table>
<thead>
<tr>
<th>Description</th>
<th>Groups</th>
<th>Dietary cholesterol</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGee et al. (1984)</td>
<td>Honolulu Heart Program Study; 7088 male Japanese descendants in Hawaii; prospective cohort, 10-y follow up</td>
<td>Age-adjusted mean intake at baseline (variance data not reported). Cases: 257 mg/1000 kcal Control: 242 mg/1000 kcal</td>
<td>No significant difference between groups in baseline total cholesterol intake (mg/d), but a significant 15 mg/1000 kcal difference ((P &lt; 0.05)) was observed in baseline cholesterol density of diet between control group and cases</td>
</tr>
<tr>
<td>McGee et al. (1985)</td>
<td>Same as above</td>
<td>Total cholesterol intake at baseline ranged from &lt; 300 mg/d to &gt; 900 mg/d             Ten-year, age-adjusted rate of death (per 1000) from CHD was not significantly related to baseline total cholesterol intake (mg/d) but was related to cholesterol density (mg/kcal). Deaths (per 1000) from CHD range: 8 in those having baseline cholesterol intake &lt;125 mg/1000 kcal to 19 in those having baseline intake &gt;325 mg/1000 kcal ((P &lt; 0.05))</td>
<td></td>
</tr>
<tr>
<td>Kushi et al. (1985)</td>
<td>Ireland-Boston Diet-Heart Study; Prospective cohort of 1001 men in Ireland or the United States, 20-y follow up; adjusted for age and cohort</td>
<td>Mean baseline cholesterol intake ± SEM: 266 ± 8 mg/1000 kcal (853 mg/d) in cases All others: 248 ± 3 mg/1000 kcal (832 mg/d)</td>
<td>18 mg/1000 kcal difference ((P &lt; 0.03)) in baseline cholesterol intake between cases and all others</td>
</tr>
<tr>
<td>Tell et al. (1994)</td>
<td>Atherosclerosis Risk in Communities Study in four regions in the United States; this report utilized 83% of baseline cohort</td>
<td>Mean ± SD cholesterol intake (mg/d): Black women: 247 ± 128 White women: 219 ± 103 Black men: 311 ± 160 White men: 268 ± 140</td>
<td>Ultrasound measures of carotid wall thickness were not significantly associated with cholesterol intake in men. After adjustment for age and energy intake, women at the 75(^{th}) percentile of cholesterol intake had 0.015 mm greater carotid artery wall thickness than women at the 25(^{th}) percentile of cholesterol intake ((P &lt; 0.01); values for 25(^{th}) and 75(^{th}) percentiles of intake not reported) [follow-up to 1998 by Chambless et al. (2002) did not re-examine the association of outcomes with cholesterol intake]</td>
</tr>
</tbody>
</table>

(Continued next page)
### Table II-3. Six studies cited by Institute of Medicine (2005a) as supporting a positive association between dietary cholesterol and CHD.  

<table>
<thead>
<tr>
<th>Description</th>
<th>Groups</th>
<th>Dietary cholesterol</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Watts et al. (1994)</strong></td>
<td>St. Thomas’ Atherosclerosis Regression Study: 50 U.K. men referred for coronary angiography because of angina pectoris or myocardial infarction, not requiring revascularization</td>
<td>Diet: education with goal of cholesterol intake of 100 mg/1000 kcal (n=26)</td>
<td>Cholesterol intake was assessed two or more times in study period</td>
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<tr>
<td></td>
<td>Control: usual care (n=24)</td>
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<td>Cholesterol intake (mean ± SEM) did not differ significantly across three response groups:</td>
</tr>
<tr>
<td></td>
<td>These groups were merged, then divided by change in disease</td>
<td>Progression of disease (n=10): 349 ± 39 mg/d (152 mg/1000 kcal)</td>
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<tr>
<td></td>
<td></td>
<td>No change in disease (n=32): 258 ± 18 mg/d (124 mg/1000 kcal)</td>
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<tr>
<td></td>
<td></td>
<td>Regression of disease (n=8): 255 ± 39 mg/d (127 mg/1000 kcal), where change was measured as minimum absolute width of coronary segments via angiography from baseline to approximately 39 months later</td>
<td></td>
</tr>
<tr>
<td><strong>Mann et al. (1997)</strong></td>
<td>Prospective observation of 9980 U.K. subjects, healthy at baseline; ~13-year follow up; adjusted for age, sex, smoking, and social class</td>
<td>Deaths from IHD (n=64) Deaths from other causes (n=328) Survivors (n=9588)</td>
<td>Cholesterol intake was assessed at baseline. Tertile cholesterol intake for men (mg/d):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1st: 0 to 214 2nd: 214-345 3rd: 345+</td>
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<tr>
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<td></td>
<td>Tertile cholesterol intake for women (mg/d):</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1st: 0 to 196 2nd: 196-291 3rd: 291+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45 deaths from IHD and 265 deaths from other causes by tertile of cholesterol intake as follows:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1st: 8 IHD deaths; 108 other causes 2nd: 15 IHD deaths; 75 other causes 3rd: 22 IHD deaths; 82 other causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cholesterol intake was unknown for 19 who died from IHD and for 63 who died from other causes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Significant trend for increased death from IHD from the 1st to 3rd tertile of cholesterol intake, yet there was a significant decrease in all-cause mortality from the 1st to 2nd tertile of cholesterol intake</td>
</tr>
</tbody>
</table>

CHD: Coronary heart disease; IHD: ischemic heart disease; IOM: Institute of Medicine
In several of the studies, IOM identified dietary variables other than cholesterol that were positively (e.g., saturated fat) and negatively (e.g., fiber) associated with cholesterol intake and CHD. Thus, other variables can confound the interpretation of cholesterol results in studies that do not control for these factors.

IOM reasoned that although the effects of dietary cholesterol are highly variable among individuals and are attenuated at higher baseline intakes, in general:

1. A 100 mg/d increase in dietary cholesterol leads to a 0.05 to 0.1 mmol/L (1.9 to 3.9 mg/dL) increase in blood total cholesterol;
2. Approximately 80% of the increase in blood total cholesterol is in the LDL fraction, (e.g., 0.04 to 0.8 mmol/L);
3. Such an increase in LDL-cholesterol would lead to a 1% to 2% increase in CHD (references not cited).

Due to the limited power of epidemiological studies to detect a 1% to 2% increase in CHD from changes in dietary cholesterol, IOM (2005a) concluded that existing epidemiological data “did not provide a meaningful basis for establishing adverse effects of dietary cholesterol.”

**II.2.4 Effects of dietary cholesterol on blood lipoproteins**

Based on reports of the Baltimore Longitudinal Study of Aging (Sorkin et al., 1992), the Multiple Risk Factor Intervention Trial (Neaton & Wentworth, 1992; Stamler et al., 1986), and the Zutphen Elderly Study (Weijenberg et al., 1996), IOM regarded the relationship of blood total cholesterol to CHD risk and mortality as progressive. IOM therefore used the effects of dietary cholesterol on blood lipoproteins as the basis for its conclusions regarding the association of dietary cholesterol and cardiovascular disease. The serious hazard that IOM identified as related to high cholesterol intake was increased blood lipoproteins, “which would be predicted to result in increased risk for CHD.”

IOM reviewed 50 studies published from 1960 to 1998 that examined the lipoprotein response to dietary cholesterol. Of these reports, 32 examined the blood response after adding dietary cholesterol to “defined” diets and 18 examined the response of adding dietary cholesterol to self-selected diets. In these studies, the effects of cholesterol intake ranging from 0 to 585 mg/d were compared to effects after supplementing these diets with additional cholesterol in amounts ranging from 7 to 4800 mg/d. Most of these studies tested responses at extremely high cholesterol intakes; less than one-half (21 of 50) included measures of blood cholesterol associated with changing dietary cholesterol by 500 mg/d or less. IOM compiled a table containing “baseline” dietary cholesterol intakes, the amounts of cholesterol added to the diets, and the changes in blood total cholesterol (Institute of Medicine, 2005a). The relationship between changes in dietary cholesterol and changes in blood total cholesterol concentration are depicted in Figures II.1 and II.2 [IOM (2005a) Figures 9-2 and 9-3]. The corrected equation of the line for the defined diets is \( y = 0.0008x + 0.1592 \) \((R^2 = 0.1869)\) using the value of 330 mg/d for a Keys et al. (1965a) data point rather than the 33 mg/d error in Table 9-2 of the IOM (2005a) report.
Figure II.1. Linear relationship between change in cholesterol intake (0 to 1,100 mg/d) from defined or self-selected diets and change in blood total cholesterol concentration (Institute of Medicine, 2005a), showing corrected equation of the line for defined diets (see footnote 6).

Figure II.2. Logarithmic relationship between change in cholesterol intake (0 to 4,800 mg/d) from defined or self-selected diets and change in blood total cholesterol concentration (Institute of Medicine, 2005a).
IOM (2005a) reported that of the studies it reviewed, none examined the effects of very small incremental changes in dietary cholesterol in numbers of subjects large enough to permit statistical treatment of the data to define the lowest level of cholesterol intake shown to increase total or LDL-cholesterol concentration (i.e., the lowest-observed-adverse-effect level). IOM cited Wells and Bronte-Stewart (1963) as indicating that adding as little as 17 mg of dietary cholesterol to a cholesterol-free diet coincided with a rise in blood total cholesterol of 0.44 mmol/L (17.7 mg/dL) in three subjects, which IOM approximated from a data figure. Wells and Bronte-Stewart (1963) tested the rise in blood total cholesterol by adding incremental supplements of dietary cholesterol to a maize and white bread diet containing 17 mg/d of cholesterol. They reported no significant difference in blood cholesterol when egg white replaced dietary casein, decreasing cholesterol intake to nearly zero.

Wells and Bronte-Stewart (1963) concluded that the range of intake of cholesterol where an effect on blood total cholesterol was observed was between 40 and 500 mg/d. Using the equations generated by IOM from its review (Table II-4), the addition of 17 mg dietary cholesterol is estimated to increase blood total cholesterol by 0.19 mmol/L (7.2 mg/dL) or 0.02 mmol/L (0.7 mg/dL) based on “defined” and self-selected diets, respectively.

IOM (2005a) also considered several published meta-analyses of experimental feeding studies and the resulting predictive formulas (Table II-4). IOM suggested that the Hopkins (1992) predictive formula is supported by McMurry et al. (1985), in which blood total cholesterol increased from 2.92 to 3.8 mmol/L for Tarahumara Indians of Mexico after dietary cholesterol was increased from 0 to 905 mg/d. Actually, those data were reported earlier by McMurry et al. (1982) and included by Hopkins (1992) in the data that were used to generate the Hopkins equation.

IOM stated, “on average, an increase of 100 mg/d of dietary cholesterol is predicted to result in a 0.05 to 0.1 mmol/L increase in blood total cholesterol.” The IOM equations based on defined and self-selected diets (Table II-4) produced estimates of a 0.25 mmol/L (10 mg/dL) and a 0.05 mmol/L (2 mg/dL) change in blood total cholesterol, respectively, after addition of 100 mg/d cholesterol to the diet. It is not clear how IOM derived its stated average of 0.05 to 0.1 mmol/L.

IOM recognized that the baseline cholesterol intake level can influence the intensity of the response to alterations in dietary intake. For example, using the Hopkins (1992) equation, an increase from zero baseline intake to 100 mg/d dietary cholesterol is predicted to result in an increase of 6 mg/dL (0.16 mmol/L) total blood cholesterol, whereas adding 100 mg/d to a baseline intake of 300 mg/d is predicted to increase blood total cholesterol by 1.9 mg/dL (0.05 mmol/L). Many predictive equations do not account for the level of baseline dietary cholesterol.

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6Note that Table 9-2 [page 553 of the IOM report (2005a)] states that a 33 mg/d change in dietary cholesterol elicited a 0.41 mmol/L (15.9 mg/dL) change in blood total cholesterol for 22 patients as reported by Keys et al. (1965a; 1965b). However, the value 33 is a transcription error from the actual 330 mg/d (rounded from 328) change in intake. It is not known whether this error was used by IOM to generate its Figures 9-1 and 9-2. Also, an alternate interpretation of the Keys et al (1965a; 1965b) reports would be that the baseline intake was 380 mg/d and both the change in dietary cholesterol (380 to 50 mg/d) and the change in blood response were negative (i.e., a decline).
Table II-4. The estimated change in blood total cholesterol in response to changes in cholesterol intake derived from reports of meta-analyses reviewed by the Institute of Medicine (2005a).

<table>
<thead>
<tr>
<th>Source</th>
<th>Description</th>
<th>Baseline Cholesterol Intake (mg/d) in Database</th>
<th>Examples of Change in Dietary Cholesterol (mg/d)</th>
<th>Estimated Change in Blood Total Cholesterol (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hegsted (1986)</td>
<td>14 studies; changed dietary cholesterol by 29 to 400 mg/1000 kcal; excluded outliers having very low responses. y mg/dL = 0.0974x where x=change in mg/1000 kcal</td>
<td>0 – 400 mg/1000 kcal</td>
<td>+100 to 400 (40 to 160 mg/1000 kcal)</td>
<td>+ 0.10 to 0.40 (~ 4 to 16 mg/dL)</td>
</tr>
<tr>
<td>Hopkins (1992)</td>
<td>27 controlled-feeding studies, weighted by number of participants per study. y mmol/L = 1.22(e^{-0.0035x})(1 - e^{-0.0015x}) where x=baseline mg/d; x=change in mg/d (p &lt; 0.0005, r = 0.617)</td>
<td>0 – 400 mg/d</td>
<td>+100 to 400 from baseline of 0 mg/d</td>
<td>+ 0.16 to 0.51 (~ 6 to 20 mg/dL)</td>
</tr>
<tr>
<td>Howell et al. (1997)</td>
<td>224 studies weighted by number of participants per study and number of multiple observations per group. The best fitting prediction model (n=177 study groups) included changes in dietary saturated fat and polyunsaturated fat in addition to dietary cholesterol (p &lt; 0.0005, R^2 = 0.736); for each 1 mg change in dietary cholesterol, blood total cholesterol changes by 0.57 mmol/L (or 0.022 mg/dL).</td>
<td>Not reported</td>
<td>±100 to 400</td>
<td>± 0.06 to 0.23 (~ 2 to 9 mg/dL)</td>
</tr>
<tr>
<td>Clarke et al. (1997)</td>
<td>Solid food studies; healthy volunteers. Univariate analyses: 395 experiments (72 published studies); for each 1 mg change in dietary cholesterol, blood total cholesterol changes by 0.0013 (SE 0.0002) mmol/L.</td>
<td>Not reported</td>
<td>-100 to -400</td>
<td>-0.13 to -0.52 (~ 5 to 20 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Multivariate analyses: 227 experiments (&lt;72 published studies; number not reported); for each 1 mg change in dietary cholesterol, blood total cholesterol changes by 0.0007 (SE 0.0001) mmol/L.</td>
<td>Not reported</td>
<td>-100 to -400</td>
<td>-0.07 to -0.28 (~ 3 to 11 mg/dL)</td>
</tr>
<tr>
<td>Wegge-mans et al. (2001)</td>
<td>17 studies, weighted by number of participants per study. (Predictions reported for two changes in intake, 100 and 200 mg/d)</td>
<td>Not in model</td>
<td>+100</td>
<td>+ 0.05±0.005 (2.2± 0.19 mg/dL) (mean±SEE)</td>
</tr>
<tr>
<td></td>
<td>(Predictions reported for two changes in intake, 100 and 200 mg/d)</td>
<td></td>
<td>+200</td>
<td>+ 0.11±0.010 (4.3±0.4 mg/dL)</td>
</tr>
<tr>
<td>Institute of Medicine (2005a)</td>
<td>27 reports of defined diets. Change in blood total cholesterol (y) resulting from change in dietary cholesterol (x) up to 1100 mg/d: y (mmol/L) = 0.0008x + 0.1737^a</td>
<td>0 – 400 mg/d</td>
<td>+100 to 400</td>
<td>0.25 to 0.49 (~ 10 to 19 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>15 reports of self-selected diets. Change in blood total cholesterol (y) resulting from change in dietary cholesterol (x) up to 1100 mg/d: y (mmol/L) = 0.0004x + 0.0108</td>
<td>120 – 585 mg/d</td>
<td>+100 to 400</td>
<td>0.05 to 0.17 (~ 2 to 7 mg/dL)</td>
</tr>
</tbody>
</table>

^Corrected equation is y = 0.0008x + 0.1592 (R^2 = 0.1869) and change in blood total cholesterol of 0.24 to 0.48 mmol/L (9 mg/dL to 18.5 mg/dL).
IOM limited its discussion to the effects of adding dietary cholesterol and did not specify which, of the studies it reviewed, if any, had reported the effects of decreasing dietary cholesterol from baseline intake. Hence, an underlying assumption of the IOM interpretation is that for any given baseline intake, bi-directional changes in dietary cholesterol (e.g., add or subtract 100 mg/d of cholesterol) exert effects of similar magnitude on blood cholesterol.

IOM (2005a) ascertained that for any one individual, the response of blood total cholesterol to dietary cholesterol is relatively consistent but this response might be modulated by other factors in the diet. For example, IOM noted that some investigators, but not others, reported that low intake of saturated fat and high intake of polyunsaturated fat can blunt the effect of dietary cholesterol on blood total cholesterol.

IOM also acknowledged the substantial evidence of wide inter-individual variation in blood lipid responses to dietary cholesterol, which might be due in part to individual differences in cholesterol absorption and hepatic synthesis. Considering data from animal models, IOM recognized that variations in several human genes might be contributing to differences in dietary cholesterol response among individuals. For example, IOM discussed common variants of the \textit{ABCG5} and \textit{ABCG8} genes that enhance cholesterol absorption.

### Low density lipoprotein cholesterol

IOM (2005a) stated, there is much evidence to indicate a positive linear trend between cholesterol intake and low density lipoprotein cholesterol concentration, and therefore increased risk of CHD. It went on to note that because increased dietary cholesterol, on average, increased blood concentrations of both high density lipoprotein and LDL-cholesterol, the net effect on cardiovascular disease risk might depend on the relative changes in these lipoproteins, as well as on other unmeasured mediators of atherogenesis.

IOM discussed the evidence of blood LDL-cholesterol response to dietary cholesterol in relation to three papers: Hegsted \textit{et al.} (1993), Clarke \textit{et al.} (1997), and Dreon & Krauss (1997). IOM cited Hegsted \textit{et al.}'s (1993) suggestion that increased blood total cholesterol in response to increasing dietary cholesterol is due primarily to increased blood LDL-cholesterol. From a collection of approximately 50 metabolic studies, Hegsted \textit{et al.} (1993) constructed datasets of 248 observations for blood total cholesterol and 155 values for LDL-cholesterol. Hegsted \textit{et al.} (1993) produced the following regression equations, where blood concentration is in mmol/L, co-variants of fat intake are expressed as the percentage of energy, and dietary cholesterol is expressed as ng/J:

\begin{itemize}
  \item $\Delta$ blood total cholesterol = 2.10 ($\Delta$ dietary saturated fatty acid) – 1.16 ($\Delta$ dietary polyunsaturated fatty acid) + 0.067 ($\Delta$ dietary cholesterol)
  \item $\Delta$ blood LDL-cholesterol = 1.74 ($\Delta$ dietary saturated fatty acid) – 0.766 ($\Delta$ dietary polyunsaturated fatty acid) + 0.0439 ($\Delta$ dietary cholesterol)
\end{itemize}

Hegsted \textit{et al.} (1993) concluded that diet-induced changes in LDL-cholesterol “roughly parallel” and “approximate” changes in blood total cholesterol.

IOM further stated that approximately 80% of the increase in blood total cholesterol in response to changes in dietary cholesterol is in the LDL fraction (Institute of Medicine, 2005a). The estimate of 80%, although not specifically cited, is consistent with IOM’s discussion of Clarke \textit{et al.} (1997). Of the 72 reports included by Clarke \textit{et al.} (1997) for meta-analysis, a subset of 227
solid food experiments reported LDL-cholesterol (the total number of subjects was not reported). For some studies, Clarke et al. (1997) estimated mean cholesterol intake from median or mid-range values. Multivariate regression coefficients (SE) of effects per each mg/d of cholesterol in the diet were 0.0007 (0.0001) for blood total cholesterol and 0.0005 (0.0001) for LDL-cholesterol (71% of total response). IOM referred to Clarke et al. (1997) as predicting an increase of 0.05 mmol/L (1.9 mg/dL) in LDL-cholesterol in response to the addition of 100 mg/d of dietary cholesterol. Further multivariate analyses by Clarke et al. (1997) indicated that isocaloric changes to replace 10% of dietary saturated fat by polyunsaturated fat (5%) and monounsaturated fat (5%) and to decrease cholesterol intake by 200 mg (e.g., 340 mg/d to 140 mg/d) was estimated to reduce blood total cholesterol by 0.76 mmol/L (SE 0.03, 99% confidence interval 0.67 to 0.85) or 29.4 mg/dL, including a reduction in LDL-cholesterol of 0.62 (0.04) mmol/L or 24 mg/dL (82% of total response). Clarke et al. (1997) suggested that “in the average British diet, replacement of 60% of the saturated fat by other dietary fats and avoidance of 60% of dietary cholesterol would reduce blood cholesterol by about 0.8 mmol/L (that is, by 10-15%), with four fifths of this reduction being in low density lipoprotein cholesterol,” (i.e., attributing 80% of the blood cholesterol decline to LDL-cholesterol).

IOM cited Dreon & Krauss (1997) as indicating that apolipoprotein genetic variants (i.e., apo E polymorphism) have been associated with increased blood LDL-cholesterol in response to dietary saturated fat and dietary cholesterol in some, but not all, studies.

IOM (2005a) concluded that there was a positive linear trend between cholesterol intake and LDL-cholesterol concentration from data showing an increase in blood total cholesterol after the addition of dietary cholesterol and based on the relationship between total and LDL-cholesterol. Moreover, IOM concluded that “any incremental increase in cholesterol intake increases CHD risk.” As mentioned above, IOM expects that an increase in LDL-cholesterol of 0.04 to 0.8 mmol/L, resulting from adding 100 mg/d of cholesterol to the diet, would lead to approximately a 1% to 2% increase in CHD (data not cited), noting that the effect is attenuated at higher baseline cholesterol intakes.

**II.2.5 Institute of Medicine recommendations**

In its hazard identification, IOM considered that increasing dietary cholesterol will increase blood total cholesterol (and LDL-cholesterol), “which would be predicted to result in increased risk for CHD.” From its dose-response assessment of dietary cholesterol, IOM (2005a) suggested that a very low intake level of dietary cholesterol, a level exceeded by most diets, may increase risk of CHD (not cited and no evidence discussed of CHD risk at low levels of cholesterol intake). IOM cited Wells and Bronte-Stewart (1963), who indicated that as little as 17 mg/d of dietary cholesterol might raise blood total cholesterol, and acknowledged that only three subjects were examined. IOM suggested that substantially greater added amounts (i.e., 100 mg/d) could lead to an increase in LDL-cholesterol that would be associated with a 1% to 2% increase in CHD (data not cited). Using the risk assessment model, IOM was unable to derive a Tolerable Upper Intake Level for cholesterol because neither a no-observed-adverse-effect level nor a lowest-observed-adverse-effect level could be determined. It reasoned that “any incremental increase in cholesterol intake increases CHD risk.”

IOM concluded, “any incremental increase in cholesterol intake increases CHD risk.” IOM recommended that cholesterol consumption be as low as possible while consuming a
nutritionally adequate diet; IOM issued the same recommendation for intake of trans fat and saturated fat.

IOM cautioned that without proper planning, the elimination of all cholesterol in the diet might have the undesirable effect of overly restricting protein and certain micronutrients. IOM cited a study by Janelle & Barr (1995) in which the diets of vegan (n=8) and omnivorous (n=22) women in western Canada were compared. Vegans consumed significantly less cholesterol (94 versus 231 mg/d), protein (52 versus 77 g/d), vitamin B12 (0.51 versus 3.79 mg/d), riboflavin (1.32 versus 1.72 mg/d), and calcium (578 versus 950 mg/d) than nonvegetarians. Average intake by vegans of vitamin B12, calcium, and zinc was inadequate and intake of protein and riboflavin was borderline-adequate compared to the RDA. Nonetheless, IOM decided that nutritionally adequate, low cholesterol diets were possible. IOM (2005b) provided a few suggestions for minimizing cholesterol intake such as reducing the frequency of intake and serving size of cholesterol-rich foods (e.g., liver, eggs)\(^7\) and egg-containing foods, and selecting lean meats and low-fat dairy products.

In responding to an editorial by Colombani (2006), who questioned the rationale used by the DRI Committee to recommend that dietary cholesterol be as low as possible, Kris-Etherton (2006) asserted that dietary cholesterol modestly influences LDL-cholesterol. She emphasized that the recommendation to keep cholesterol intake as low as possible should be viewed in concert with other dietary strategies, all together contributing to a total risk reduction of cardiovascular disease. By suggesting that dietary cholesterol is “an important a la carte side dish,” not the entrée at the meal, Kris-Etherton underscored the DRI Committee expectation that the elimination of dietary cholesterol was unrealistic for most Americans although necessary for some who are most susceptible to its adverse effects. Kris-Etherton then referred Colombani (2006) to the Dietary Guidelines for Americans (U.S. Department of Agriculture, 2005e), written for the general public, which recommend cholesterol intake of less than 300 mg/d or less than 200 mg/d if LDL-cholesterol is elevated.

**Further research**

IOM concluded that more clinical research is needed to ascertain clearly defined levels of dietary cholesterol at which significant risk can occur for adverse health effects (e.g., onset of CHD). It recognized the wide inter-individual variation in LDL-cholesterol response to dietary cholesterol and remarked that more information is needed on factors contributing to individual variation. IOM made six specific recommendations for cholesterol research:

1. Determine molecular mechanisms regulating absorption of dietary cholesterol
2. Define the dose-response of dietary cholesterol and blood LDL-cholesterol from low intake to high intake
3. Delineate specific genetic variants contributing to inter-individual differences in the response of blood LDL-cholesterol to dietary cholesterol
4. Delineate non-cholesterol components of diet and other factors that contribute to interindividual differences in response of blood LDL-cholesterol to dietary cholesterol
5. Determine the relationship between cholesterol intake and body pools of cholesterol

\(^7\)The Institute of Medicine reported older data for the cholesterol content of one egg (250 mg) versus the most up-to-date value of 212 mg.
6. Identify possible mechanisms whereby cholesterol intake during early development might affect adult atherosclerosis

II.3 DIETARY GUIDELINES FOR AMERICANS

Federal dietary guidelines are intended to provide the most current diet and health advice for the general public to promote healthy diets and reduce risk for major chronic diseases. They pertain to individuals who are at least two years of age. By law, each federal agency is required to promote U.S. dietary guidelines when carrying out federal food, nutrition, and health programs (McMurry, 2003). For example, the Nutrition Labeling and Education Act of 1990 (NLEA) required manufacturers to provide nutrition labeling for most foods (except meat and poultry). For labeling purposes, the amount of cholesterol in milligrams per serving must be included in the Nutrition Facts panel (U.S. Food and Drug Administration, 1999). Also required on the label, cholesterol per serving must be expressed as a percentage of the Daily Value (upper limit of 300 mg). The Daily Value for cholesterol is the same for all levels of calorie intake. As specified in §101.9 (c) of NLEA, the percentage of the “Daily Value” of cholesterol provided by a food is determined from the Daily Reference Value that the FDA established for fats. FDA chose the 300 mg cut-off because it was consistent with the recommendations issued one year earlier in the National Research Council’s report *Diet and Health: Implications for Reducing Chronic Disease Risk* (National Research Council, 1989a). (See Appendix C.) This cut-off corresponded to the recommendations of other health organizations, such as the AHA and the NCEP (U.S. Food and Drug Administration, 1996). The Division of Nutrition Programs and Labeling at FDA is developing an advanced notice of proposed rulemaking to be published in late 2006 or early 2007 for public comment on the Nutrition Facts panel, which contains the Daily Values.

II.3.1 Twenty-six year history

The first edition of the dietary guidelines was published in 1980. The focus at that time was to translate scientific evidence into a message emphasizing the health benefits of eating a variety of foods, particularly recommending foods containing dietary fiber and complex carbohydrates (Schneeman, 2003). Cautionary advice has since been incorporated in dietary guidelines to limit the public’s consumption of sugar, fat, saturated fat, cholesterol, sodium, and alcohol. As mandated by law in 1990 (7 U.S.C. 5341), the dietary guidelines are reviewed jointly by DHHS and USDA every five years (U.S. Department of Agriculture, 2005e). That legislation has since expired, but review and revision efforts continue (Dwyer, 2006). In 1992, the USDA and DHHS released the first version of *The Food Guide Pyramid* (the Pyramid), to echo the nutrition education messages in the dietary guidelines in a graphic format. The Pyramid replaced the USDA’s older box-type food group format. Continuing development and revision of the Pyramid and dietary guidelines aim to incorporate new scientific findings and sharpen perceptions and understanding so that consumers make healthier food selections.

The 1995 edition of the dietary guidelines (U.S. Department of Agriculture, 2005a) initiated a numerical goal for cholesterol. It referred to the 300 mg Daily Value for cholesterol in the Nutrition Facts panel on food product labels and suggested keeping cholesterol intake at or below this level by eating more grain products, vegetables and fruits, and by limiting intake of

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8 Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition (FDA)
high cholesterol foods. By 2000, dietary guidelines were expanded to include messages about food safety and physical activity, and highlighted the value of whole grains, fruits, and vegetables by encouraging daily intake of these beneficial foods. In its report, the 2000 Dietary Guidelines Advisory Committee (DGAC) stated that it “supports the 1995 recommendation that Americans should limit intake of dietary cholesterol and specifies 300 mg per day a value that is consistent with the recommendations of authoritative bodies” (U.S. Department of Agriculture, 2000a). The dietary fat summary in the 2000 Guideline was: “Choose a diet that is low in saturated fat and cholesterol and moderate in total fat.” The 2000 DGAC recommended the following wording for the consumer guideline materials, “Following the tips in the box above will help you keep your intake of saturated fat at less than 10% of calories and your cholesterol intake less than 300 mg/d.” However, the final version was worded, “Following the tips in the box above will help you keep your intake of saturated fat at less than 10% of calories. They will also help you keep your cholesterol intake less than the Daily Value of 300 mg/d listed on the Nutrition Facts Label.” This slight wording change shifted the independent 2000 DGAC recommendation to one of encouraging compliance with the same recommendation made by FDA.

The current edition of the dietary guidelines, Nutrition and Your Health: Dietary Guidelines for Americans (Guidelines), was released in January 2005 (U.S. Department of Agriculture, 2005e).

**Monitoring compliance to dietary guidelines**

Through development of the Healthy Eating Index (HEI) using Pyramid servings, the USDA Center for Nutrition Policy and Promotion attempted to gauge the effectiveness of its public health nutrition messages (Guthrie & Smallwood, 2003). The HEI, which included a measure of total cholesterol intake (Component 8), has been applied to all national nutrition CSFII survey data since 1989 to examine changes in U.S. intake. The HEI has also been applied to federal food programs to determine whether such programs are consistent with national guidelines (Willett & Stampfer, 2006). Measures of diet quality are being used in epidemiological studies to examine links between patterns of intake, level of adherence to national dietary guidelines, and risk of chronic disease.

In the HEI, a total cholesterol consumption of 300 mg/d or less was assigned the best score for dietary cholesterol based on the 1989 recommendations of the Committee on Diet and Health (National Research Council, 1989a). (See Appendix C.) During 1999 and 2000, this cut-off for cholesterol intake was met by 69% of the U.S. population surveyed (Basiotis et al., 2006).

The HEI has been further revised and expanded to include 10 components, providing scores that better reflect recommended dietary variety, modification, and proportionality (i.e., Diet Quality Index–Revised) (Haines et al., 1999). In the revised index, the cholesterol content of the diet is scored 10 if the diet meets the dietary guideline of 300 mg/d or less cholesterol, 5 for intake between 300 and 400 mg/d, and 0 for greater than 400 mg/d (Haines et al., 1999).

**II.3.2 Revision process leading to 2005 guidelines**

Dietary guidelines are updated in a three-step process, relying on the work of DGAC. DGAC is composed of medical and academic experts selected by the Secretaries of DHHS and USDA for their scientific knowledge of the relationship between dietary intake and health. Members of
DGAC work under the regulations of the Federal Advisory Committee Act. The role of DGAC is solely advisory and its activities are time-limited (U.S. Department of Agriculture, 2005d).

In the first step of the revision process, DGAC was to prepare a scientific report of evidence for the Secretaries of DHHS and USDA. For the most recent update, DGAC reviewed the 2000 edition of the dietary guidelines (U.S. Department of Agriculture, 2000b) to determine if, on the basis of the preponderance of current scientific and medical knowledge, any revision was warranted. The DGAC report was to contain any nutrition and health revisions DGAC deemed necessary along with relevant evidence.

To prepare the scientific report, subcommittees of DGAC were formed to address key messages, such as fat intake. Midway through the review process, a Macronutrient Subcommittee and a Science Review Subcommittee were formed to address cross-cutting topics and to help maintain consistent standards for the subcommittee reviews. The voluntary status of the DGAC membership placed much of the burden of amassing relevant data upon federal staff and/or temporary consultants (Dwyer, 2006). Staff developed the search strategy in consultation with the chairs of the subcommittees. The search strategy specified exact search parameters, terms, databases, and inclusion criteria (e.g., dates of publication). In its review of the primary literature, DGAC placed the greatest emphasis on results from cohort studies and trials with well-accepted, clinically relevant outcomes (U.S. Department of Agriculture, 2005d). Such outcomes included clinical diseases (e.g., myocardial infarction) and well-accepted risk factors (e.g., LDL-cholesterol). Meta-analyses were also considered. The conclusions reached reflected the consensus of the entire DGAC group (U.S. Department of Agriculture, 2005d).

In the second step to update dietary guidelines, USDA and DHHS deliberated jointly to arrive at key recommendations based on the DGAC scientific report, and took into consideration input presented from citizens and industry representatives during public comment periods (Dwyer, 2006) (U.S. Department of Agriculture, 2005e). Current food availability and consumption patterns were examined to understand how these might hinder compliance with the proposed guidelines (Dwyer, 2006).

In the third and final step, the Departments consulted with communication experts to format recommendations for the general public. The draft Guidelines were tested with nonscientists for consumer comprehension and practicality. The final wording of the Guidelines was crafted by experts in communication to present the key messages in a format that would best convey these recommendations to the general public (U.S. Department of Agriculture, 2005e).

**II.3.3 Evidence report for dietary cholesterol guideline**

With the release of the Guidelines, the USDA also made available the scientific report of the DGAC, which contains technical information describing the data upon which the Guidelines were developed (U.S. Department of Agriculture, 2005e).

**Sources of data**

A substantial amount of the scientific data reviewed by DGAC were identified in the first issue of the IOM report *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002). Specifically, DGAC reported that it examined the
LSRO Report: Approach to Establish Guidelines for Cholesterol Intake

IOM review of 50 controlled trials and 15 observation studies, reporting the association of cholesterol intake and blood cholesterol and/or CHD, which formed the basis for the DRI recommendation for dietary cholesterol.

DGAC also examined the evidence-based review of cholesterol in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (see Appendix B) (National Heart, Lung, and Blood Institute, 2002). DGAC considered the NCEP recommendation that dietary cholesterol be restricted to below 200 mg/d for individuals meeting NCEP criteria for Therapeutic Lifestyle Changes (e.g., LDL-cholesterol greater than 130 mg/dL (National Heart, Lung, and Blood Institute, 2002). DGAC also considered the recommendation of the American Diabetes Association (ADA) for persons with diabetes to restrict dietary cholesterol to less than 300 mg/d and its suggestion that diabetic individuals with LDL-cholesterol at 100 mg/dL or higher may benefit from restricting dietary cholesterol to less than 200 mg/d (Franz et al., 2004).

DGAC included in its review five additional, more recent controlled trials, which it did not identify (U.S. Department of Agriculture, 2005d). One might deduce from the bibliography that Knopp et al. (2003) was among the five recent trials reviewed and/or it is possible that DGAC relied on the review by Grundy et al. (2004) of five clinical trials of statin therapy, which extended NCEP’s 2002 review efforts. Thus, DGAC considered the scope of its review to include at-risk populations of adults with elevated LDL-cholesterol of 130 mg/dL or higher.

DGAC also considered data from food modeling exercises as well as the historical precedence of cholesterol recommendations of 300 mg/d endorsed more than one-quarter century ago by AHA (American Heart Association Committee on Nutrition, 1968; Inter-Society Commission for Heart Disease Resources, 1970) and the U.S. Senate Select Committee on Nutrition and Human Needs (1977).

Cholesterol intake and heart disease

DGAC posed the following question: What are the relationships between cholesterol intake and cardiovascular disease?

DGAC reiterated points made by IOM (2002; 2005a), that epidemiologic observations are confounded by saturated fat, energy intake, and fiber intake. The only data DGAC presented on the relationship between cholesterol intake and CHD were in its discussion of trans fat. DGAC mentioned the analysis of food composites representing average intakes of middle-aged men in the Seven Countries Study by Kromhout et al. (1995). This study showed a positive association between 25-year mortality rates from CHD and the average intake of dietary cholesterol (in mg/1000 kcal; \( r = 0.55, P < 0.05 \)) and also showed cholesterol intake correlated with saturated fat intake (\( r \geq 0.62, P < 0.05 \)). The association between average intake of saturated fatty acid or trans fatty acid and death rate from CHD were stronger (\( r \geq 0.78, P < 0.001 \)) than that of dietary cholesterol.

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9IOM reviewed 32 published reports of dietary cholesterol added to defined diets and another 18 of dietary cholesterol added to self-selected diets with strict control of intake. IOM reviewed 15 published reports of dietary cholesterol and CHD incidence. (See Sections II.2.3 and II.2.4, above.)
DGAC considered ADA’s recommendations to restrict cholesterol intake for persons with diabetes, which were informed by two studies (Franz et al., 2002). First, Hu et al. (1999) suggested that consumption of one or more eggs per day appeared to be associated with increased risk of CHD compared with less frequent egg consumption among individuals with diabetes, but cautioned that these findings were produced by numerous subgroup analyses and further research was warranted. Second, although studies of specific dietary cholesterol restriction in diabetic patients were not available, a meta-analysis of 37 intervention studies using low-fat diets, most with dietary cholesterol restriction, demonstrated that low-fat diets have been effective in eliciting changes in blood total cholesterol and LDL-cholesterol in other individuals (Yu-Poth et al., 1999). Yet, individuals with marked elevations in blood lipids were less responsive to dietary interventions than were mildly to moderately hypercholesterolemic individuals (Yu-Poth et al., 1999).

IOM expects that any incremental increase in dietary cholesterol will increase CHD risk. IOM estimated that an increase in LDL-cholesterol of 0.04-0.8 mmol/L would lead to approximately a 1% to 2% increase in CHD (data not cited). Citing IOM (2002) and NCEP (National Heart, Lung, and Blood Institute, 2002), DGAC also expected that if dietary cholesterol caused a 0.8% to 1.2% increase in LDL-cholesterol, it would increase CHD risk about 1%.

DGAC focused on a summary by NCEP of Grundy et al. (1988), who examined the evidence from epidemiological (e.g., Framingham) and clinical (i.e., Lipid Research Clinics Coronary Primary Prevention Trial) studies. Grundy et al. (1988) indicated that for every 1 mg/dL change in blood total cholesterol, the risk of CHD changes in the same direction by approximately 1%. To ascertain the health benefits of intervention, they estimated that for a diet of 2000 to 2500 kcal/d, reducing dietary cholesterol from 500 mg/d to 300 mg/d (e.g., a reduction between 100 mg/1000 kcal and 80 mg/1000 kcal) would decrease blood total cholesterol by approximately 5 to 10 mg/dL. Similarly, NCEP estimated that such a reduction in blood cholesterol might lead to a reduction in coronary risk of 5% to 10% and that such a decline would be clinically relevant for the population at large. Based on category A1 evidence (major randomized controlled clinical trials), NCEP regards a 1% reduction in LDL-cholesterol (from any treatment), on average, as reducing risk for “hard” CHD events (myocardial infarction and CHD death) by approximately 1%.

Consistent with IOM and NCEP, DGAC’s rationale for restricting dietary cholesterol can be summarized as (U.S. Department of Agriculture, 2005d):

A. Increases in blood cholesterol are expected to increase the risk of CHD progressively. Because dietary cholesterol can raise blood LDL-cholesterol, higher intakes of dietary cholesterol could raise the risk of CHD

B. Reducing cholesterol intakes from high to low could decrease blood LDL-cholesterol and decrease the risk of CHD in most persons

**Cholesterol intake and blood cholesterol**

The role that dietary cholesterol may play in affecting blood cholesterol is the foundation for USDA’s recommendations for cholesterol intake. DGAC referred to data depicted by IOM (2002; 2005a) to describe the response of blood cholesterol to cholesterol intake (see Figures II.1 and II.2). DGAC concluded that in most studies, as dietary cholesterol increases there is a corresponding increase in blood total cholesterol.
Citing a meta-analysis of 27 controlled feeding studies by Hopkins (1992), DGAC estimated that adding 100 mg/d of dietary cholesterol would raise blood total cholesterol by 5 mg/dL if baseline intake is zero or raise it by “1.5 mg/d” [sic] if baseline intake is 300 mg/d (Table II-4). In general, for baseline intake not specified, DGAC used the prediction equations of Clarke et al. (1997), Hegsted (1986), and Howell et al. (1997) to estimate that adding 100 mg/d of dietary cholesterol would increase blood total cholesterol by 2 to 3 mg/dL. This is actually more conservative than the estimate by Hegsted (1986) in which altering the diet by 100 mg/d would be predicted to change blood total cholesterol by 4 mg/dL (Table II-4).

DGAC calculated that if blood total cholesterol concentration were 200 mg/dL, a 2 to 3 mg/dL increase represented a 1% to 1.5% increase. Of this increase, DGAC regarded approximately 80% to be in the LDL fraction (i.e., a 0.8% to 1.2% increase in LDL-cholesterol). The estimate of 80% is similar to that of the IOM and is probably based on the meta-analyses of Clarke et al. (1997), who generated multivariate regression coefficients of 0.0007 for blood total cholesterol and 0.0005 for LDL-cholesterol per each mg/d of cholesterol in the diet.

DGAC recognized that the effect of added cholesterol is variable among individuals, and some individuals have essentially no response. This variability may be due to differences in baseline cholesterol intake as well as genetic and metabolic differences. DGAC pointed to a study showing that insulin resistance and obesity seem to be related to a diminished response to dietary cholesterol (Knopp et al., 2003). In this randomized, double-blind cross-over trial, 197 subjects were fed a placebo or 2 or 4 eggs per day for four weeks. Baseline blood total and LDL-cholesterol were significantly higher in the insulin-resistant groups compared to the insulin-sensitive group. After ingestion of four eggs per day, LDL-cholesterol rose significantly in insulin-sensitive (7%) and normal weight insulin-resistant individuals (3%), but did not significantly change in obese insulin-resistant individuals (Knopp et al., 2003).

Based on the collective evidence, DGAC concluded that the magnitude of response of blood cholesterol is much less for dietary cholesterol than that observed for saturated and trans fat intake, and noted also that research on the effects of dietary cholesterol on LDL-cholesterol in healthy children is lacking.

**Consumption data and data generated by food modeling**

In making its recommendations, DGAC recognized that mean cholesterol intake from 1999 to 2000 was 341 mg/d in men and 242 mg/d in women. In children and adolescents, peak intake of 375 mg/d in boys was reached between 16 to 19 years of age and peak intake of 233 mg/d in girls was reached between 9 to 11 years of age. Among males aged 12 to 19 years, the mean (but not median) intake exceeded 300 mg/d regardless of racial/ethnic group.

At DGAC's request, USDA's Center for Nutrition Policy and Promotion used food modeling exercises to examine whether food patterns with different fat intakes and energy levels would meet science-based criteria for a healthful diet (U.S. Department of Agriculture, 2005d). Through these exercises DGAC learned that energy intakes of 2,800 kcal or higher in which 35% of calories were from fat could pose a problem for heart health because dietary cholesterol was above the standard of 300 mg. Specifically, calorie patterns of 2,800, 3,000, and 3,200 contained 310, 314, and 319 mg of cholesterol, respectively (U.S. Department of Agriculture, 2005b). Thus, DGAC cautioned that particular attention must be paid to keeping cholesterol intake at or
below the recommended limit of 300 mg/d for diets providing more than 30% of calories from fat.

DGAC did not discuss whether it examined how the IOM (2002; 2005a) recommendation to consume as little dietary cholesterol as possible might alter essential nutrient intake. Food modeling of vegan diets devoid of animal products would help to address this issue. Such an analysis, if conducted, was not reported. However, the USDA did model lacto-ovo vegetarian diets to identify appropriate ratios of legumes, nuts, and eggs to meet nutrient needs and to assess what additional modifications in vegetarian food choices would be necessary (U.S. Department of Agriculture, 2005c). In this analysis, the recommended milk group servings were left unchanged, with two or three cups of milk per day included in the various intake patterns. The percent milkfat was not reported except for the diet patterns of young children, in which whole milk was used.

Compared to food patterns that include meat, fish, and poultry, the cholesterol and saturated fat contents of lacto-ovo vegetarian food patterns are substantially reduced. The lacto-ovo vegetarian patterns used in the food modeling exercises met vitamin, mineral, and macronutrient requirements at all 12 calorie levels for all age/sex groups. However, actually obtaining sufficient amounts of iron, vitamin E, and potassium may prove to be challenging for some vegetarians. Recommended intakes of lysine (considered the most limiting essential amino acid in vegetarian diets) were met by determining the protein available in both animal (eggs and milk) and plant (nuts, legumes, grains) products. The suggested egg intake for vegetarians ranges from 5 to 7 eggs per week, depending on energy requirements (Table II-5). Hence, based on food-modeling exercises, the lowest cholesterol intake recommended by the USDA in a lacto-ovo vegetarian diet that meets energy and nutrient recommendations would be approximately 159 to 212 mg/d.

**Table II-5. Daily and weekly intake of eggs recommended by energy level for lacto-ovo vegetarians**

<table>
<thead>
<tr>
<th>Energy intake (kcal)</th>
<th>Suggested daily egg intake</th>
<th>Suggested weekly egg intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1800</td>
<td>~3/4</td>
<td>~5</td>
</tr>
<tr>
<td>2200</td>
<td>~1</td>
<td>~6</td>
</tr>
<tr>
<td>2800</td>
<td>~1</td>
<td>~7</td>
</tr>
</tbody>
</table>

Adapted from: Table G2-6. Daily and Weekly Intake Recommendations for ENL Intake Patterns (U.S. Department of Agriculture, 2005c). Note that for purposes of calculating nutrient intake of vegetarians, the animal and plant protein food group consists of eggs, nuts, and legumes (ENL) whereas for omnivores, this food group consists of meat, poultry, fish, eggs, and nuts (MPFEN).

### II.3.4 Guideline recommendations

Because DGAC concluded that “the relationship between cholesterol intake and LDL-cholesterol concentrations is direct and progressive, increasing the risk of CHD,” it recommended that cholesterol intake should be kept as low as possible, within a nutritionally adequate diet. In particular,

- For adults with an LDL-cholesterol below 130 mg/dL, less than 300 mg/d of dietary cholesterol is recommended
- For adults with an elevated LDL-cholesterol of 130 mg/dL or higher, less than 200 mg/d of dietary cholesterol is recommended
DGAC recommended that intakes of saturated fat and trans fat should be decreased, and saturated fat should be the primary focus of dietary modification because saturated fat consumption is proportionately much greater than that of cholesterol and trans fats. The key 2005 cholesterol recommendation summary for individuals two years of age and older was, “Consume less than 10% of calories from saturated fatty acids and less than 300 mg/day of cholesterol, and keep trans fatty acid consumption as low as possible” (U.S. Department of Agriculture, 2006a).

Given its approach to updating the dietary guidelines, the decision by the 2005 DGAC to retain the threshold of 300 mg/d recommended by the 2000 DGAC was likely due to a lack of convincing evidence that some other value was more feasible to further reduce risk of CHD. Furthermore, there is a historical basis for the use of 300 mg/d as it has been recommended in U.S. dietary guidelines since 1995. The selection by DGAC of the specific cut-off value of 200 mg/d for hypercholesterolemic individuals was not explained, but was likely adopted from similar cut-offs advocated by NHLBI (National Heart, Lung, and Blood Institute, 2000) and the ADA (Franz et al., 2004), whose reports were cited by DGAC.

As an example of how the USDA cholesterol recommendation of < 300 mg/d might be translated into a diet, one might consume approximately one egg (210 mg), 1 oz cheese or one cup of 2% milk (20 mg), and 3 oz of fish, lean beef, lean pork, or light-meat turkey (50-70 mg) and comply with dietary recommendations (U.S. Department of Agriculture, 2006c). Consumer materials at MyPyramid (U.S. Department of Agriculture, 2006e) inform the public of foods high in cholesterol (egg yolks, liver, and giblets) to limit as well as encourage consumption of a variety of foods.

II.4 SUMMARY OF U.S. DIETARY RECOMMENDATIONS

The primary line of reasoning used by the USDA and IOM for its recommendations that the general public restrict cholesterol intake is that elevated blood cholesterol, particularly LDL-cholesterol, is associated with CHD and dietary cholesterol can increase blood cholesterol.

The statement by IOM (2005a) that “any incremental increase in cholesterol intake increases CHD risk” coupled with its recommendation that cholesterol consumption be as low as possible while consuming a nutritionally adequate diet was considered by USDA in developing dietary guidelines for the public (Table II-6). Based on food-modeling exercises, USDA (2005d) calculated that the lowest recommended cholesterol intake in a lacto-ovo vegetarian diet that met essential nutrient recommendations would be approximately 160 to 212 mg/d, depending on level of energy requirements.

The USDA’s continued use of a daily cut-off value for dietary cholesterol of 300 mg/d for the general population was not explained. Given the charge of DGAC, this status quo was likely continued because there was insufficient evidence to suggest that some other value would be more advantageous and feasible.

The next issue of U.S. dietary guidelines is planned for 2010.
Table II-6. Summary of current U.S. recommendations for dietary cholesterol (abridged from Appendix D)

<table>
<thead>
<tr>
<th>Authoritative Source</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>USDA; DHHS <em>Dietary Guidelines for Americans</em> (2005)</td>
<td>Cholesterol intake should be kept as low as possible, within a nutritionally adequate diet. Less than 300 mg/d of dietary cholesterol is recommended for adults with an LDL-cholesterol &lt; 130 mg/dL and less than 200 mg/d of dietary cholesterol is recommended for adults with an elevated LDL-cholesterol of ≥130 mg/dL. Based on food-modeling exercises, the lowest cholesterol intake recommended in a lacto-ovo vegetarian diet (that met energy and essential nutrient recommendations) would be approximately 160 to 212 mg/d</td>
</tr>
<tr>
<td>IOM <em>Dietary Reference Intakes</em> (2005)</td>
<td>Cholesterol consumption should be as low as possible while consuming a nutritionally adequate diet. A Tolerable Upper Intake Level was not set</td>
</tr>
<tr>
<td>FDA <em>The Food Label</em> (1999)</td>
<td>The Daily Value is less than 300 mg. Cholesterol per serving must be expressed on food labels as a percentage of the Daily Value (uppermost limit of 300 mg)</td>
</tr>
</tbody>
</table>

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III. RECOMMENDATIONS OF OTHER NATIONS AND THE WORLD HEALTH ORGANIZATION

III.1 AUSTRALIA

III.1.1 Overview

Anglo-Celtic and Aboriginal foods are traditional in Australia. In the last two decades, the variety of the Australian diet has expanded primarily influenced by the influx of Vietnamese and other Asians and by increased availability of fresh, processed, and prepared foods in the marketplace (National Health and Medical Research Council, 2003b). National Nutrition Survey data indicate that cholesterol intake decreased from 1983 to 1995 by 14% in men and 22% in women, and was unchanged from 1985 to 1995 in children (National Health and Medical Research Council, 2003b). The average intake of total fat as a percentage of energy ranged from 31% in older men to 34% in girls eight to eleven years of age (National Health and Medical Research Council, 2003b). The average intake of saturated fat as a percentage of energy ranged from 12% in middle-aged women to 16% in girls two to three years of age.

In Australia, national nutrition guidelines and nutrient reference standards fall under the jurisdiction of the National Health and Medical Research Council (NHMRC), a statutory body responsible to the Commonwealth Minister for Health and Ageing. Within the NHMRC, the National Health Committee functions primarily to develop and provide evidence-based guidelines or other forms of advice on nutrition and a range of other public health matters in support of health promotion and illness prevention. Diet and health reports published by prominent Australian public and medical groups are listed in Table III-1.

The dissemination of public health information has been coordinated and otherwise assisted by the National Public Health Partnership (NPHP) of the Chief Health Officers of the Commonwealth, States and Territories; the Chair of the NHMRC; and the Director of the Australian Institute of Health and Welfare. To provide strategic direction and coordinate action specifically on nutrition issues, a national partnership of government authorities known as the Strategic Inter-Governmental Nutrition Alliance (SIGNAL) began in 1998 as the nutrition arm of the NPHP (Australian Government Department of Health and Ageing, 2003). SIGNAL was developed and guided by the national public health nutrition strategy and action plan Eat Well Australia 2000-2010, which includes an action plan for Aboriginal and Torres Strait Islander nutrition. This broad, long-range strategy focuses on four nutrition priorities: preventing overweight and obesity; increasing the consumption of vegetables and fruit; promoting optimal nutrition for women, infants, and children; and improving nutrition for vulnerable groups. It does not specifically address dietary cholesterol.

National dietary guidelines serve as tools to support the outcomes identified in Eat Well Australia 2000-2010. NHMRC has only funded and endorsed guidelines that were developed through approved processes. In April 2006 the framework and cost estimate for a national nutrition monitoring and surveillance system were proposed to support guideline development and other initiatives (Masters et al., 2006). One of the central proposals in this framework was to reinstate the collection and reporting of Apparent Consumption of Foodstuffs in Australia from 2000/03, to be conducted every five years for data on macronutrient (e.g., fat) consumption. It did not specify a need for measures of dietary cholesterol.
As of June 2006, the NPHP and the National Health Priority Action Council Expert Advisory Groups are defunct and have been replaced by the Australian Population Health Development Principal Committee. This committee is comprised of senior health development and health service officials from each jurisdiction in Australia (National Public Health Partnership Secretariat, 2006). The new advisory structure aims to make health advice to Australian jurisdictions more effective and timely, especially by integrating prevention strategies across all aspects of chronic disease management. The Secretariat for the new Principal Committee will be provided through the Department of Health and Ageing.

**Table III-1. A selection of Australian publications addressing diet and cardiovascular disease**


**Assessment and application of scientific evidence**

The process for generation and revision of dietary guidelines in Australia includes evidence-based development, consultation, review, and independent assessment. The following principles served to direct guideline development (Baghurst, 2003):

- They should seek to promote the benefits of healthful eating, not only to reduce the risk of diet-related diseases but also to improve the community’s health and well being
- They should be consistent with Australian Food and Nutrition Policy for good nutrition, ecological sustainability, and equity
- They should apply to the total diet; they should not be used to assess the healthfulness of individual food items, nor should individual guidelines be considered in isolation
- They should be evidence-based
- The process of review should be consultative
The expert groups tasked to revise dietary guidance documents use the evaluation system developed by the Food Standards Australia New Zealand (FSANZ) to categorize the evidence it considers (Baghurst, 2003) (Table III-2). FSANZ initially developed this classification system for use in evaluating evidence for food or health claims (National Health and Medical Research Council, 2006a).

### Table III-2. The National Health and Medical Research Council (2006a) designation for six levels of evidence in scientific reviews

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of all relevant randomized controlled trials</td>
</tr>
<tr>
<td>II</td>
<td>At least one properly-designed randomized controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>Well-designed pseudo-randomized controlled trials (alternate allocation or some other method)</td>
</tr>
<tr>
<td>III-2</td>
<td>Comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case-control studies, or interrupted time series with a control group</td>
</tr>
<tr>
<td>III-3</td>
<td>Comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group</td>
</tr>
<tr>
<td>IV</td>
<td>Case series, either post-test or pretest/post-test</td>
</tr>
</tbody>
</table>

### III.1.2 Australia and New Zealand Nutrient Reference Values

To arrive at the 2005 nutrient reference intakes, an Expert Working Party was appointed to revise the 1991 *Recommended Dietary Intakes for Use in Australia*. Working Party members included the following representatives: one consumer representative, one industry representative, one expert in Aboriginal and Torres Strait Islander nutrition, one pediatric expert, a representative of the Royal College of General Practice, and other public health and nutrition experts (Baghurst, 2003). However, rather than use the 1991 guidelines as the starting point, the Working Party was to assign experts to review the Dietary Reference Intakes (DRI) established by the United States and Canada (Institute of Medicine, 2002), then advise the NHMRC on the suitability of transferring these values for use in Australia and New Zealand (National Health and Medical Research Council, 2006b). The reviewers were asked to provide an evidence-based assessment of the key papers used in the DRI document. Reviewers were also asked to review the guidelines of other influential countries and the World Health Organization (WHO), and to identify other relevant data published more recently or missing from other reviews.

For each DRI recommendation (U.S./Canadian), the reviewers were to recommend either adoption; adoption with minor changes; adoption with substantial changes; or rejection, for use in Australia and New Zealand; and to summarize their overall recommendations. Thus, references to DRI, including the DRI for lipids (Institute of Medicine, 2002), are interwoven into the final 2005 recommendations and supporting documents (National Health and Medical Research Council, 2006b).
**Recommendations**

The revised *Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes* were endorsed and published by the NHMRC (National Health and Medical Research Council, 2006b). A minimum fat intake of 20% of energy was recommended to sustain body weight and allow for estimated average requirements of micronutrients. After considering evidence on the potential influence of excess dietary fat on body weight and cardiovascular complications, an upper limit of 35% of energy as fat was recommended for the general population, in agreement with the U.S./Canadian DRI. This upper limit approximates the 60th percentile of intake in the Australian and New Zealand national surveys for adults (i.e., 60% of adults surveyed had intakes of total fat at or below 35% of energy) (National Health and Medical Research Council, 2006b). Based on the association with markers of risk for coronary heart disease (CHD), it was further recommended that the combined intake of saturated and trans fats be limited to 10% of energy. Other than to mention that dietary cholesterol was not essential, cholesterol intake was not discussed (National Health and Medical Research Council, 2006b).

**III.1.3 Dietary guidelines**

Australia’s dietary guidelines were designed to encourage a healthy diet and lifestyle that will minimize the risk of diet-related diseases. The guidelines are prepared by federal and academic health and nutrition science experts, assembled as a Working Party, to assess the evidence of the efficacy of nutrients and food components in relation to specific health outcomes. NHMRC published the first set of adult dietary guidelines in Australia in 1979 (Baghurst, 2003), which was developed separately from guidelines in New Zealand. The 1992 revision was a set of 10 guidelines that included calcium-rich and iron-rich foods. NHMRC has endorsed the third, current edition for adults (National Health and Medical Research Council, 2003b).

Dietary guidelines for Australian adults are listed in Table III-3. Each guideline deals with a priority health issue. The guidelines are no longer listed by number because each guideline is considered equally important. They make recommendations for some risk-related nutrients, such as limiting saturated fat and moderating total fat intake. Dietary cholesterol is not specifically addressed. The current guidelines focus more on food groups than previous editions, and encourage consumption of lean meats and reduced-fat dairy products (National Health and Medical Research Council, 2003b).

A separate guideline for older Australians, issued in 1999, was rescinded in December 2005. A dietary guideline for children and adolescents introduced in 1995 was revised in 2003 to incorporate infant feeding guidelines for health workers (National Health and Medical Research Council, 2003a). It is noted in the pediatric guideline that reduced-fat milks are not suitable for those under two years of age (National Health and Medical Research Council, 2003a).

Technical, evidence-based background papers prepared by members of the Working Party for use by health professionals were published alongside the consumer-oriented dietary guidelines. The technical documents include a written rationale for each guideline (National Health and Medical Research Council, 2003b).
The Commonwealth Scientific and Industrial Research Organization (2005; 2006) is Australia's national science agency. Its consumer information sheets state:

- It is probably safe for most people with normal blood cholesterol to eat eggs in moderation
- People with high blood cholesterol levels should restrict egg consumption
- The most effective way to lower cholesterol is to reduce animal fats in the diet

Table III-3. The Dietary Guidelines for Australian Adults (National Health and Medical Research Council, 2003b)

Enjoy a wide variety of nutritious foods:
- Eat plenty of vegetables, legumes and fruits
- Eat plenty of cereals (including breads, rice, pasta and noodles), preferably wholegrain
- Include lean meat, fish, poultry and/or alternatives
- Include milks, yoghurts, cheeses and/or alternatives. Reduced-fat varieties should be chosen, where possible
- Drink plenty of water

and take care to:
- Limit saturated fat and moderate total fat intake
- Choose foods low in salt
- Limit your alcohol intake if you choose to drink
- Consume only moderate amounts of sugars and foods containing added sugars

Prevent weight gain: be physically active and eat according to your energy needs

Care for your food: prepare and store it safely

Encourage and support breastfeeding

III.1.4 Rationale for adult guidelines

Truswell (2003) prepared the background information for the development of the adult guidelines related to fat intake. Regarding the overall guideline to limit saturated fat and total fat intake, he determined there was Level III evidence (Table III-2) from 15 metabolic trials of the effects of various dietary fats on blood cholesterol, Level II and III evidence from 10 controlled intervention trials for the effects of type of dietary fat on CHD, and Level III evidence from 14 other prospective studies and two biomarker case-control studies.

To date, NHMRC’s position on dietary cholesterol has been that, at the public health level, advice to reduce saturated fat will bring with it lower cholesterol intakes since these two lipid classes usually occur in the same foods. Moreover, Truswell (2003) explained that the Australian dietary guidelines focus on saturated fat rather than dietary cholesterol because the cholesterol-elevating effect of dietary cholesterol is considered less consistent than that of saturated fats. Truswell cites the reviews by Beynen & Katan (1989) and Bronte-Stewart (1958), several controlled experiments and meta-analyses (Clarke et al., 1997; Hegsted et al., 1965; Hegsted et al., 1993; Keys et al., 1957; Mensink & Katan, 1992), and position statements on dietary fats by the National Heart Foundation (NHF) (National Heart Foundation's Nutrition and Metabolism Advisory Committee, 1999a; 1999b) as supporting the appropriateness of the focus
on saturated fat, in that saturated fat is the strongest dietary determinant of low density lipoprotein (LDL)-cholesterol.

Truswell cited Hu et al. (1999) as supporting the consumer directive to focus on saturated fat rather than dietary cholesterol. Hu et al. (1999) examined the association between egg consumption and risk of CHD and reported that the consumption of up to one egg a day was not associated with any significant increase in the rate of CHD or stroke among healthy men and women. However, it was of concern that among individuals with diabetes, consumption of one or more eggs per day appeared to be associated with increased risk of CHD. Hu et al. (1999) cautioned that this finding was produced by numerous subgroup analyses and further research with diabetic patients was warranted.

Data from the Hu et al. (1999) report coupled with the prevalence of elevated blood cholesterol in the Australian population appear to be the rationale for Truswell’s suggestion of eating, at most, one egg per day, whole or in prepared dishes, as a practical means to incorporate the dietary guidelines into everyday life and to optimize the fat profile of the diet (National Health and Medical Research Council, 2003b).

**Review papers - evidence for adult guidelines**

Apart from studies by Connor et al. (1961a; 1961b; 1964), which enrolled six healthy men per study, Beynen & Katan (1989) were not aware of controlled long-term studies with dietary cholesterol as the only experimental variable. In their review, Beynen & Katan (1989) cited Keys et al. (1965a) and other early reports characterizing how blood cholesterol concentration changes after cholesterol intake is altered. Using the equation developed by Keys et al., (see p. 26) they predicted that adding 500 mg/d of cholesterol to a “moderate-cholesterol” diet of 240 mg/d without changing protein or fat intake would result in blood total cholesterol increasing an average of 11.3 mg/dL (0.29 mmol/L), about 6%, depending on what food the cholesterol-containing food replaces in the diet. Although the responsiveness of blood cholesterol is less pronounced at higher cholesterol intakes, Beynen & Katan (1989) concluded that there is no plateau of blood concentration at which dietary cholesterol is no longer influential. Based on some of their own investigations, they further concluded that blood cholesterol is influenced by the cumulative cholesterol content of the diet in the previous two weeks but not by the previous meal. They cautioned that chance and/or poor adherence to treatment may explain variability in responses rather than a “hyporesponder” factor.

Beynen & Katan (1989) cited the results of the National Diet-Heart Study (American Heart Association, 1968d) as demonstrating that the ratio of polyunsaturated to saturated fat intake can alter the blood response to dietary cholesterol. In their report, they summarized a portion of this dataset but did not describe which study diets, which intake (planned diet or observed intake), which sites (5 cities, one institution), which times, or which subgroups they combined. They concluded that the dietary-cholesterol-induced increase in blood cholesterol was somewhat smaller on a diet high in polyunsaturated fat than on a diet high in saturated fat.

They suggested that, in general, the single most powerful intervention to lower blood cholesterol was replacement of saturated fat by polyunsaturated fat, with a caveat that individual fatty acids exert different effects on blood cholesterol. To arrive at this conclusion, they considered three long-term studies in which saturated fat was replaced by polyunsaturated fat and was associated with a 12 to 15% decline in blood cholesterol (Dayton et al., 1965; Leren, 1966; Miettinen et al.,
1972) and 18 shorter controlled experiments of the effects on blood lipoprotein fractions after increasing the ratio of polyunsaturated to saturated fat in man. Beynen & Katan (1989) discussed several flaws with experimental designs of diet and blood lipoprotein metabolism published at that time and made several suggestions to improve future studies.

Bronte-Stewart (1958) reviewed data on the effects of type of fat consumption on blood total cholesterol and concluded that higher animal fat intake is associated with higher blood total cholesterol among different groups in Africa and elsewhere; dietary cholesterol was not discussed.

**Controlled experiments and meta-analyses – evidence for adult guidelines**

An early report by Keys *et al.* (1957) summarized a series of studies conducted to test the effect of isocaloric diets of varying fat content on blood total cholesterol. In some diets, portions of dietary fat were replaced by carbohydrate and/or various other fats were substituted for the regular “house-diet” fat. The “house diet” contained, on average, 740 mg/d of dietary cholesterol in contrast to the lower-fat diets, which contained an average of 300 mg/d. The experimental diets were fed for two to nine weeks to 66 schizophrenic, but otherwise healthy, men, aged 32 to 62 years, and to 18 male Japanese coalminers aged 22 to 54 years. From these data, Keys *et al.* (1957) generated prediction equations and determined that saturated fats longer than 10 carbons had twice as much effect in raising blood total cholesterol as polyunsaturated fatty acids had in depressing blood cholesterol. This report dispelled the notion held by some at that time that essential fatty acid deficiency was contributing to the development of hypercholesterolemia. Keys *et al.* (1957) encouraged change from the liberal use of saturated animal fat by substitution with linoleic or other polyunsaturated fats.

As discussed in section II.1.1, Hegsted *et al.* (1965) fed egg-yolk-free diets to patients in a mental institution. Test diets were alternated every four weeks with control diets of the same duration. The source of added fat in the test diet was coconut oil, olive oil, or safflower oil. The blood response to dietary cholesterol was similar for each of the three different diets, an average increase of approximately 5 mg/dL per 100 mg of dietary cholesterol (supplied by meat). Hegsted *et al.* (1965) concluded that dietary cholesterol produced a small, positive effect on blood cholesterol, but saturated fat intake accounted for 72% of the variation in blood total cholesterol concentrations, and polyunsaturated fatty acid intake had an inverse relationship with blood cholesterol.

Mensink & Katan (1992) conducted a meta-analysis of 27 trials published between 1970 and 1991 in which dietary cholesterol was held constant but the intakes of saturated fat, monounsaturated fat, and polyunsaturated fat varied across experimental groups. Thus, the results pertain to changes in blood cholesterol in response to changes in fatty acid intake not dietary cholesterol. They stated that the number of studies for which cholesterol intake could be calculated (n=16) was too small to permit their examination of this factor. The most favorable lipoprotein risk profile for CHD was achieved when saturated fats were replaced by unsaturated fats, with no decrease in total fat intake.

Hegsted *et al.* (1993) constructed a dataset of 248 observations for blood total cholesterol and a dataset of 155 values for LDL-cholesterol (see section II.2.4). From regression analysis, they generated prediction equations for blood cholesterol based on intake of saturated fat, polyunsaturated fat, and dietary cholesterol. They concluded that saturated fat is the primary
determinant of blood cholesterol and that the diet-induced changes in LDL-cholesterol “roughly parallel” and “approximate” changes in blood total cholesterol. Nevertheless, they advised that because dietary cholesterol also increases blood cholesterol, it must be considered when the effects of fatty acids are evaluated.

Clarke et al. (1997) generated multivariate regression coefficients of 0.0007 for blood total cholesterol and 0.0005 for LDL-cholesterol per each mg/d of cholesterol in the diet (see section II.2.4 and Appendix B). The effects of saturated fat on total blood cholesterol and LDL-cholesterol were greater, with regression coefficients of 0.052 for blood total cholesterol and 0.036 for LDL-cholesterol per unit change in saturated fat as percent of total calories. Clarke et al. (1997) suggested that “in the average British diet, replacement of 60% of the saturated fat by other dietary fats and avoidance of 60% of dietary cholesterol would reduce blood cholesterol by about 0.8 mmol/L (that is, by 10-15%), with four fifths of this reduction being in low density lipoprotein cholesterol” (i.e., attributing 80% of the blood cholesterol decline to LDL-cholesterol).

National Heart Foundation position statements

To develop its position statements, members of NHF’s Nutrition and Metabolism Advisory Committee (1999b) considered the relationship between fat intake and clinical end points for cardiovascular disease. The NHF Committee (1999a) found it difficult to determine the association between dietary cholesterol and coronary endpoints because it regarded changes in dietary cholesterol as typically accompanied by other confounding dietary changes such as altered saturated fat intake. Moreover, the NHF Committee recognized that individual responsiveness and baseline dietary cholesterol also may influence the intensity of the response and confound results (Clifton et al., 1990; 1992; Katan et al., 1988a; Katan et al., 1988b). The NHF Committee (1999a) noted that most published studies reported dietary effects on blood total cholesterol but not on lipoprotein fractions. Thus, it determined there was insufficient evidence to predict the effect of dietary cholesterol on the ratio of total cholesterol to high density lipoprotein (HDL)-cholesterol or on LDL-cholesterol concentrations. Based on the published review and prediction equations of Hopkins (1992), it estimated that reducing dietary cholesterol by 100 mg/d would result in a reduction in blood total cholesterol of 0.035 to 0.069 mmol/L (1.4 to 2.7 mg/dL) and that reductions would derive mainly from lowering LDL-cholesterol. The NHF Committee was aware of one report of a positive association between dietary cholesterol and CHD in cohort studies (Stamler & Shekelle, 1988) that had not yet been confirmed in primary or secondary prevention trials. It surmised that little was known at that time about the effects of dietary cholesterol on other risk factors and endpoints such as blood pressure, insulin resistance, overweight, thrombosis, and arrhythmia.

The resulting consensus recommendations were intended for the general population and for high risk individuals. The NHF Committee (1999a) provided a quantitative target for dietary saturated fats and trans fatty acids, together to contribute no more than 8% of total energy intake, but a quantitative target was not specified for dietary cholesterol. Based on what the NHF Committee (1999b) considered “moderate evidence” it concluded that dietary cholesterol increases total blood cholesterol and LDL-cholesterol, particularly in sensitive individuals, but substantially less so than saturated and trans fatty acids; contributes to the development of CHD; and that it may be prudent to restrict dietary cholesterol in hypercholesterolemic individuals. Thus, it was recommended that individuals who are at low coronary risk can reasonably eat moderate
quantities of cholesterol-rich foods, and those with plasma cholesterol greater than 5.0 mmol/L (193 mg/dL) or with other risk factors should restrict their intake of cholesterol-rich foods.

At the time Truswell (2003) prepared the background document for the dietary guidelines (National Health and Medical Research Council, 2003b), he noted that the NHF Committee (1999b) was recommending that individuals with blood total cholesterol greater than 5 mmol/L (193 mg/dL) or with other risk factors should restrict intake of cholesterol-rich foods. Truswell remarked that over one-half of the adult Australian population had blood total cholesterol concentrations above this level.

Similarly, in subsequent publications, NHF of Australia (2004) did not recommend that the general population restrict consumption of eggs, but for those individuals at risk of CHD or living with heart disease, it recommended altering the types of fat in the diet (i.e., limiting saturated fat), and discussing intake of egg yolks with a doctor or accredited dietitian. Dietary education efforts to prevent secondary cardiovascular events in individuals with CHD include the recommendation to limit cholesterol-rich foods such as egg yolks and offal (liver, kidney, brains) (National Heart Foundation Australia and Cardiac Society of Australia and New Zealand, 2004). The position statements on lipid management were updated recently (National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand, 2005). These position statements advised the general population as well as high-risk individuals to follow a low saturated fat diet, incorporate moderate amounts of polyunsaturated fats and oils in their diet, include at least 2 g of plant omega-3 fatty acid (alpha linolenic acid) per day, consume marine omega-3 via two or three fish meals per week, and select a wide variety of fruits, vegetables and whole grain cereal products.

III.1.5 Rationale for pediatric guidelines

The final pediatric guideline, “Limit saturated fat and moderate total fat intake,” was the same as the corresponding adult guideline except for the additional qualifier that, “Low-fat diets are not suitable for infants.” The background evidence for the pediatric guideline for dietary fats was prepared by Davidson (2003). Davidson also commented on reports of negative dietary behaviors learned in childhood, such as an excessive intake of saturated fats, and the potential long-term consequences of these behaviors.

Davidson reviewed recommendations and rationales for fat intake issued by numerous other countries and organizations. Among this evidence, he cited autopsy studies showing that early coronary atherosclerosis or its precursors can begin in childhood and that the extent of the lesions in childhood is correlated with blood cholesterol concentration. He was aware of many trials with cholesterol-lowering drugs that confirmed the importance of blood cholesterol in CHD, even in individuals having blood cholesterol concentrations at average U.S. values.

Since many foods with a significant fat content are rich in nutrients and are important components of a healthy diet, Davidson was particularly concerned over the safety of diets designed to decrease consumption of fat and cholesterol in growing children. He cited a report of growth failure in eight children associated with overly restrictive, inadequate dietary treatment of hypercholesterolemia (Lifshitz & Moses, 1989). Of these eight children, three had nutritional dwarfing characterized by a markedly reduced rate of linear growth, cessation of weight gain, and lack of progression in sexual maturity. Once nutrition intervention (diet counseling and monitoring) was provided, patients gained weight at a rate of 4 to 7 kg/year, and grew 6 to 7.6
cm/year while blood cholesterol decreased by 10% to 28%. Davidson categorized as Level IV (Table III-2) the evidence that growth failure can result from low-fat, low-cholesterol diets in young children.

Davidson (2003) was unable to identify any appropriately controlled trials of dietary modification in children that demonstrated a reduced incidence of CHD later in life. He categorized two reports of the Special Turku Coronary Risk Factor Intervention Project (STRIP) for Babies conducted in Finland (Lagström et al., 1997; Rask-Nissilä et al., 2000) as Level III evidence that less than typical saturated fat and cholesterol intake in children showed no deleterious effects on growth or neurological development from the age of seven months to five years. These reports described the experience of seven-month-old infants and their parents, who were recruited at well-baby clinics between 1990 and 1992 in Turku, Finland. Families were randomly assigned to receive periodic individualized counseling aimed at limiting the child's fat and cholesterol intake or to receive standard care (Rask-Nissilä et al., 2000). Among participants available for measures at five years of age (n=496), mean (SD) fat intake was lower ($P < 0.001$) for the intervention group compared to the control group for total fat [30.6% (4.5%) versus 33.4% (4.4%)] and saturated fat [11.7% (2.3%) versus 14.5% (2.4%)], as a percent of energy; and for cholesterol [164.2 mg (60.1 mg) and 192.5 mg (71.9 mg)], respectively. However, the intakes of fat by children in the intervention and control groups were markedly below values that were recommended for the first 2 years of life. Mean (SD) blood total cholesterol concentration of the intervention group was 4.27 (0.63) mmol/L [165 (24) mg/dL] and was 4.41 (0.74) mmol/L [170 (29) mg/dL] for the control group ($P < 0.05$). Measures of neurological development were not significantly different between groups (Rask-Nissilä et al., 2000).

Davidson cited Beynen & Katan (1989) as having established that the cholesterol-elevating effect of dietary cholesterol is less than that of saturated fats. Hence, the emphasis of the dietary guideline for fat intake by healthy children and adolescents in Australia is to reduce total fat, particularly saturated fat, for the purpose of preventing obesity and minimizing future chronic disease. The consumer-oriented dietary guidelines do not specifically address dietary cholesterol.

Davidson deemed it appropriate to reduce total fat, saturated fat, and dietary cholesterol, and substitute polyunsaturated and monounsaturated fats for saturated fat in diets of older children who had a strong family history of cardiovascular disease or familial hypercholesterolemia. He emphasized the need to educate parents about the importance of a well-balanced diet, taking into account the alterations needed for adequate intake of nutrients. He also suggested that the growth and development of these children should be monitored, particularly if they are prescribed a diet that replaces a portion of the fat with carbohydrate.

III.2 CANADA

III.2.1 Overview

Health Canada is the Canadian counterpart to the U.S. Department of Health and Human Services. Among its key mandates is reducing the incidence of cardiovascular disease, which is the leading cause of death in Canada. It is estimated that two out of three Canadians have one or more of the major modifiable risk factors for CHD: smoking, high blood pressure, and elevated blood total cholesterol (Brulé, 2006). Also of concern, average daily cholesterol intake among
individuals participating in the Quebec Nutrition Survey in the early- to mid-1990s indicated that men of all ages were consuming more than 350 mg/d of cholesterol (Lombardi, 1997).

The Office of Nutrition Policy and Promotion and the Food Directorate (in the Health Products and Food Branch) are the two federal groups in Health Canada responsible for Canadian dietary guidelines and food policy. The Office of Nutrition Policy and Promotion tries to influence nutritional health by issuing policies and standards for healthy eating. The Food Directorate develops regulations and guidelines related to the nutritional value and safety of foods to manage risks associated with the Canadian food supply. Diet and health reports published by prominent Canadian public and medical groups are listed in Table III-4.

**III.2.2 Recommended nutrient intakes and dietary reference intakes**

Recommended Nutrient Intakes for Canadians (RNI) were a set of scientific statements published by Health Canada that outlined essential components of the dietary pattern to prevent deficiency (Yaffe, 2004). First published in June 1938 as the Canadian national dietary standards (Ostry et al., 2006), they were revised each decade, renamed RNI in 1983 (Health and Welfare Canada, 1983) and last published in 1990 (Scientific Review Committee, 1990). These evidence-based technical documents were intended for health professionals to develop food-guide education materials for Canadian consumers. The RNI have since been superseded by DRI, which Health Canada now uses as the framework to assess and plan diets and for nutrition labeling.

The definition of the RNI, similar to that of the Recommended Dietary Allowances (RDA) in the United States, is the level of dietary intake thought to be adequate for the requirements of almost all individuals in a group with specified characteristics (age, sex, body size, physical activity), taking individual variability into account. The long-standing intent of the RNI was to meet nutrition requirements when planning diets for populations and prevent deficiency. Early RNI documents did not comprehensively address chronic disease or make recommendations concerning dietary cholesterol.

**Scientific Review Committee revises recommended nutrient intakes**

In 1987, the Department of National Health and Welfare created a new process for revising its dietary recommendations in order to further support the use of evidence-based informed decisions and to better coordinate dissemination efforts. The government appointed two advisory committees to work in partnership. The Scientific Review Committee evaluated the last two RNI (1977 and 1983) and updated recommendations for a dietary pattern that would provide sufficient nutrients and, at the same time, reduce the risk of nutrition-related chronic disease. The second advisory committee, comprising experts in communications and implementation, determined the best methods for disseminating the new RNI into actionable messages for consumers (Health Canada, 1997b).

The Scientific Review Committee enlisted nutrition experts to draft chapters that would update the RNI report for publication in 1990. The chapters underwent at least two external reviews before they were reviewed by the Scientific Review Committee (Cooper & Zlotkin, 2003). The evidence was not systematically rated. The affiliations of committee members, authors, and reviewers were not reported.
In its report *Nutrition Recommendations* the Scientific Review Committee devoted a chapter to discuss the evidence linking dietary cholesterol and atherosclerosis (Scientific Review Committee, 1990). Citing ten reports of controlled studies carried out under metabolic ward conditions and one double-blind cross-over trial, the Scientific Review Committee expressed no doubt that increasing dietary cholesterol raises blood total cholesterol in most individuals, especially if the baseline intake is low. In that chapter, the committee included available data on the effects of dietary cholesterol on specific lipoproteins and apolipoprotein fractions and what was known about adaptive mechanisms in response to excess cholesterol intake. It noted that a dietary intake of 300 mg/d or less had become the target for the general U.S. population and for 17 European countries. The Scientific Review Committee concluded that reducing the cholesterol intake of the Canadian population from the current average of 400 to 500 mg/d “towards 300 mg/d or less would be beneficial in the long-term for the reduction of mortality from coronary artery disease in this country.” However, the wording of its final recommendation in the 1990 RNI report did not specify an upper intake limit for cholesterol. Instead, it advised that cholesterol intake be reduced in all age groups of the Canadian population with the caveat that diets for infants and children be sufficient in energy and essential nutrients (Scientific Review Committee, 1990).

In its Executive Summary, the Scientific Review Committee wrote that its recommendation to consume no more than 30% of energy as total fat and no more than 10% of energy as saturated fat would lead to a general reduction in cholesterol intake. These recommendations were the same as recommendations issued two years earlier by the Canadian Atherosclerosis Society for use with at-risk patients (discussed below) (Canadian Consensus Conference, 1988). Thus in the early 1990s, the Canadian public health emphasis on dietary strategies to prevent CHD centered on total fat intake and saturated fat intake (McDonald, 2004), with supplemental recommendations for types of fatty acids and for reduction in cholesterol intake.

Cooper & Zlotkin (2003) examined the process used to arrive at Canadian dietary guidance documents and identified several shortcomings that might be improved in the future. For example, they noted that there was no mention in the documents of how the committee members were selected or whether their conflicts of interest were addressed or how committee-level decisions were made. Also not mentioned was the person(s) responsible for identifying and collecting literature and how this was accomplished. Cooper & Zlotkin (2003) concluded that a consensus approach was used by the committee for setting the 1990 RNI rather than a systematic evidence-based method because no guidance was provided to the reviewers in evaluating the literature and the literature did not have its strengths or weaknesses evaluated.

**Harmonization of reference intakes**

A 1945 attempt by Canada to adopt U.S. standards for the RDA was problematic because the two countries applied the same standard differently. Both the RDA and RNI were set at levels estimated to meet the requirements of 97.5% of their respective populations. In the United States, the RDA was applied to population groups rather than to individuals. In Canada, the RNI was used for planning both individual and group diets, but was not used to measure the adequacy of an individual’s diet (whose requirements are most likely less than the RNI amount).* As a

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10 Today, the IOM recommends that the RDA be used to plan individual intakes whereas the estimated average requirement (EAR) should be used to plan group intake. To assess adequacy of intake, the usual intake of an individual at the RDA has a low probability of inadequacy. In contrast, the EAR is used to estimate the prevalence of inadequate intakes within a group.
result, Canada reverted to the separate RNI standard in later years. By April 1995, consensus was growing among Canadian scientists that their government should evaluate the extent to which involvement with the U.S. Institute of Medicine (IOM) Food and Nutrition Board would be beneficial. As harmonization efforts in the mid-nineties advanced, regulators raised concerns with respect to the translation of nutrient requirements into food-based guidelines. Canada wondered how it might “finesse the transition without relinquishing those aspects of Canada's nutrition policy and policy development process that are valued as uniquely Canadian” (Health Canada, 1997b).

Canadian scientists now work in cooperation with the U.S. IOM Food and Nutrition Board to publish DRI, a set of reference values for nutrient intakes, which are updated periodically. As work advanced on the DRI, Canadian nutrition scientists were appointed to every committee and panel in the DRI process, leading toward a harmonized North American standard (Health Canada, 2005). As the series of DRI reports were published, they supplanted the 1989 RDA and the 1990 RNI, expanding the scope of federal dietary advice to include upper limits and nonessential components of foods. Now that the first DRI series is complete, Health Canada has entered into a contract with IOM and the National Academies to prepare a DRI Summary Report, intended for use as a reference text for health professionals (Health Canada, 2005).

See section II.2 for discussion of the IOM rationale for its latest DRI recommendation on cholesterol intake. The IOM concluded “any incremental increase in cholesterol intake increases CHD risk.” Thus it recommended that cholesterol consumption be “as low as possible while consuming a nutritionally adequate diet” (Institute of Medicine, 2005b).

Table III-4. A selection of Canadian publications addressing diet and cardiovascular disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Health Canada. Canada’s food guide to healthy eating (for people four years and older).</td>
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</table>
III.2.3 The influence of cardiovascular disease consensus groups

Committee on Diet and Cardiovascular Disease

According to Murray (1987), portions of the 1977 revision of the Canadian national dietary standards were largely adapted from a 1976 cardiovascular consensus report (Report of the Committee on Diet and Cardiovascular Disease. Ottawa, ON). The consensus report was written by an expert group of cardiologists and other specialists who convened not to develop dietary guidelines, but to advise the Canadian government on the relationship between diet and cardiovascular disease. The purpose of the Committee on Diet and Cardiovascular Disease was to determine what health claims could be made in advertisements and on labels for products such as margarine (Bush & Kirkpatrick, 2003; Murray, 1987). Instead of fulfilling this objective, the Committee devoted itself to making dietary recommendations to prevent heart disease.

The Canadian Department of National Health and Welfare (later renamed Health Canada), armed with the Report of the Committee on Diet and Cardiovascular Disease, entered into interdepartmental negotiations to gain support for use of the consensus recommendations as broader general dietary guidelines for the public. According to Murray (1987), this resulted in a few changes, the most significant of which was the deletion of all mention of cholesterol. Neither public health nutritionists nor the Canadian Department of Agriculture believed that the evidence at that time warranted the advice to curtail cholesterol to 400 mg/d and, therefore, egg intake (Murray, 1987; Murray & Rae, 1979). The Canadian Department of National Health and Welfare agreed, and all mention of dietary cholesterol was deleted before the guidelines were made public. U.S. Senators Percy, Schweiker, and Zorinsky (U.S. Senate Select Committee on Nutrition and Human Needs, 1977) pointed to this negotiated decision as an example of the divergence of scientific opinion on this issue. They remarked, “in October 1977 the Canadian Department of National Health and Welfare reversed its earlier position and concluded in a National Dietary Position that: Evidence is mounting that dietary cholesterol may not be important to the great majority of people… Thus, a diet restricted in cholesterol would not be necessary for the general population.”

The 1983 edition of the RNI (Health and Welfare Canada, 1983) briefly mentioned an association between high intakes of saturated fatty acids and elevated blood cholesterol. It was estimated that “a reduction of fat within our present dietary pattern, in which more than half of it is in an unseparated or invisible form, would decrease the intake of saturated fatty acids.” It did not make specific recommendations for dietary cholesterol.

Canadian Consensus Conference on Cholesterol

A Canadian Consensus Conference on Cholesterol (CCCC) was convened in 1988 by the Canadian Atherosclerosis Society in cooperation with the Department of National Health and Welfare to discuss how cardiovascular disease might be prevented by altering blood cholesterol (Canadian Consensus Conference, 1988).

The conference panel opted for a population strategy as well as one for individuals at high risk of cardiovascular disease (Canadian Consensus Conference, 1988). According to the report, this approach was influenced by the results of the 1986 Nova Scotia Heart Health Survey (Nova Scotia Department of Health & Department of National Health and Welfare, 1987), which suggested that approximately 71% of middle-aged and elderly Canadians may have at least one
risk factor for cardiovascular disease and that 30% of middle-aged and older Canadians may have two risk factors. The cornerstones of the conference panel’s population strategy was that food outlets should be encouraged to offer meals that are low in fat and cholesterol and that consumers should have more explicit information about the nutrient content of foods to help them select a healthy diet.

The conference panel’s recommendations for individual diet modification were designed for subgroups known to have a high incidence of hyperlipidemia, such as individuals diagnosed with CHD or who were in families with a history of early CHD, or who had known risk factors, and as such, its dietary recommendations were not specifically intended for the general public. The following basic principals were included among those advocated for high-risk patients (Canadian Consensus Conference, 1988):

- Total fat should not exceed 30% of energy intake
- Total saturated fatty acids (e.g., lauric, myristic and palmitic acids) should not exceed 10% of energy intake
- Although reducing the intake of foods containing saturated fat usually will reduce cholesterol intake as well, patients should restrict their intake of foods high in cholesterol, such as organ meats and egg yolks

The conference panel’s recommendations were consistent with the “Step I” diet in use at that time, which restricted total fat to no more than 30% of total calories, saturated fat to no more than 10% of total calories, and cholesterol to less than 300 mg/d. “Step I” and “Step II” diets were created by the National Heart, Lung, and Blood Institute’s National Cholesterol Education Program (NCEP) and were endorsed by the American Heart Association (AHA). The conference panel further advised that a portion of hypercholesterolemic patients may require more intensive dietary intervention comparable to the AHA “phase II” diet as part of their therapy to achieve target levels of blood cholesterol. The “Step II” diet goals restricted saturated fat to less than 7% of energy and dietary cholesterol to less than 200 mg/d. As of May 2001, NCEP and AHA no longer use the terms “Step I” and “Step II” in reference to heart-healthy diets, and instead refer individuals to the Therapeutic Lifestyle Changes (TLC) diet.

**Working Group on the Prevention and Control of Cardiovascular Disease**

The Working Group on the Prevention and Control of Cardiovascular Disease (the Working Group) was formed by the Federal Provincial Advisory Committee on Community Health to assess the implications of the CCCC recommendations (Canadian Consensus Conference, 1988) and to develop a public health strategy to deal with the major issues of blood cholesterol as it pertains to cardiovascular disease.

In its report *Promoting Heart Health in Canada: A Focus on Cholesterol*, which was reprinted in 1994, the Working Group decided against making a recommendation that the general public restrict its cholesterol intake (Health Canada, 1992). It suggested that in the average Canadian diet, saturated fat contributes more to elevated blood cholesterol than does dietary cholesterol. However, the Working Group advised individuals whose usual cholesterol intake is “excessive” and/or who have blood total cholesterol of 6.2 mmol/L (240 mg/dL) or greater to limit cholesterol intake to 300 mg/d.
Based on a paper by Hegsted (1986) and an unpublished monograph by Christakis (1988), the Working Group projected that a 25% reduction in dietary cholesterol from then current levels of 400 to 450 mg/d to 300 mg/d would reduce blood total cholesterol by about 0.2 mmol/L (7.7 mg/dL), or 3% to 5% for an individual having a baseline concentration of 6.2 mmol/L (240 mg/dL). The equation derived by Hegsted (1986) predicts an approximately 1 mg/dL increase in blood total cholesterol for each 1 mg/1000 kcal increase in dietary cholesterol (i.e., the change in blood total cholesterol in mg/dL is 0.0974 times the change in dietary cholesterol in mg/1000 kcal). Using the Working Group example of a 100 to 150 mg/d change in dietary cholesterol (a change of 40 to 60 mg/1000 kcal assuming a 2500 kcal/d diet), blood total cholesterol would be expected to change by 3.9 to 5.84 mg/dL (0.1 to 0.15 mmol/L) or 1.6% to 2.4% for an individual having a baseline concentration of 6.2 mmol/L, somewhat less than the Working Group estimated (Health Canada, 1992).

The Working Group cited Shekelle (1989) as indicating that dietary cholesterol may be an independent risk factor for ischemic heart disease. It also cited a personal communication from J. M. Dietschy (University of Texas, Southwestern Medical Center, 1990) as suggesting that dietary cholesterol may play an essential role in the mechanism by which saturated fats exert their effect on blood cholesterol. The Working Group referenced the (U.S.) National Research Council’s report Diet and Health (1989a), a February 1990 draft of the National Cholesterol Education Program population panel report, and a review by the Study Group of the European Atherosclerosis Society (1987) as supporting a restriction of dietary cholesterol to less than 300 mg/d.

After the initial release of the Working Group report (Health Canada, 1992), Health Canada issued its current food guide that encouraged selection of lean and lower-fat foods and reduced the serving size of eggs.

III.2.4 Food-based guides and guidelines

Fifty years of food guides: 1942 to 1992

The first consumer-oriented dietary guide, Canada’s Official Rules, was issued in 1942. It was followed by Canada’s Food Rules in 1944, then Canada’s Food Guide in 1961, and finally, Canada’s Food Guide to Healthy Eating in 1992 (Health Canada, 2002a).

Food guidance documents change over time as knowledge accumulates and as the availability of foods and nutrients in the food supply changes. Cholesterol-rich foods were featured more prominently in the early food guides. Frequent servings of liver were promoted from 1944 until 1961; then the message became “Eat liver occasionally.” By 1992, perhaps with regard to increasing concern over dietary cholesterol and other less desirable constituents of liver, recommendations for intake of liver disappeared from the food guide (Health Canada, 2002a). Similarly, in 1942, daily consumption of at least three or four eggs was encouraged. For more than thirty years, use of eggs was liberalized by including them in the meat group as an option for daily consumption accompanied by the recommendation that eggs be eaten at least three times each week. In 1977, a serving of eggs was defined as two eggs and the food guide recommended two servings of meat and alternates daily (eggs are an alternate). Yet the accompanying message to eat a variety of foods from the meat group limited egg intake to two per day. In 1992, the serving size for eggs was adjusted from two to one-to-two, whereas the number of daily servings of meat and alternates increased from two to three, again accompanied
by the directive to select a variety of foods from each food group. This message limited eggs to one or two per day.

Revisions of the Canadian food guide did not always coincide with the revisions of the RNI technical reports. For example, in 1977, both a revised RNI and a revised food guide were released but the food guide did not reflect the 1977 RNI. It was another five years before the 1977 RNI were integrated into dietary guidance materials for consumers (Bush & Kirkpatrick, 2003).

The concept of energy balance was introduced in the 1977 version of the food guide and from 1982 the concept of energy balance was given more prominence. It was recognized that minimum requirements for nutrients would need to be met in diets that also achieved optimal energy content and that avoided excessive weight gain. Also beginning in 1977, releases of the food guide were accompanied by nutrition education documents such as Canada’s Food Guide Handbook to explain the concepts underlying the main messages in the food guide. In later food guides, key messages from Health Canada’s program to promote physical activity were incorporated.

The current (1992) food guide, Canada’s Food Guide to Healthy Eating, was the first to encourage moderation in energy, fat, sugar, salt, and alcohol, a message tying diet to chronic disease (Bush & Kirkpatrick, 2003). This food guide was also the first of the Canadian food guides to specify an age of applicability (i.e., people four years of age and older) (Health Canada, 1997a). It is food-based guide, encouraging selection of lean and lower-fat foods. One serving of eggs in the meat group is identified as one-to-two eggs. In the accompanying background document, (Health Canada, 2004), it is stated that “from a dietary perspective, the key strategy for controlling blood cholesterol is to reduce the intake of total fat and, specifically, saturated fat. Dietary cholesterol, or the cholesterol found in foods, is not the main influence on blood cholesterol level, although it has some effect, in some people.” Supporting evidence was neither cited nor discussed.

In 2004, Health Canada undertook a revision of the 1992 edition of the food guide because research had shown that Canadians misinterpret and misapply some recommendations. The Office of Nutrition Policy and Promotion established an Interdepartmental Working Group to revise the food guide, and an external Food Guide Advisory Committee was created to provide advice and guidance to Health Canada throughout the revision process. The revision will be based on the DRI report, food purchasing patterns, the demographic characteristics in Canada, and reports summarizing the evidence on the relationships between select foods and their potential effect on prevention of chronic disease. It will specify the age of applicability as two years of age and older. The draft food guide is currently being developed with input from consultations, consumer focus testing, and regional meetings (Health Canada, 2006). Print and online support documents for educators will be available to accompany the revised food guide as well as a consumer-oriented website. Other nutrition-related guidelines currently under revision include Nutrition for a Healthy Pregnancy (revision began 2004) and Nutrition for Healthy Term Infants (revision began spring 2006).
Canada's guidelines for healthy eating

Health Canada developed dietary guidelines consisting of five primary messages to be communicated to Canadians over two years of age which specify limiting salt, alcohol, and caffeine but do not directly mention cholesterol although lower fat meats are encouraged (Health Canada, 2002b). This document, Canada’s Guidelines for Healthy Eating (III-2), is distinct from the similarly titled, graphic-based food guide, Canada’s Food Guide to Healthy Eating.

Table III-5. Canada’s Guidelines for Healthy Eating

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Enjoy a variety of foods</td>
</tr>
<tr>
<td>2.</td>
<td>Emphasize cereals, breads, other grain products, vegetables and fruit</td>
</tr>
<tr>
<td>3.</td>
<td>Choose lower-fat dairy products, leaner meats and food prepared with little or no fat</td>
</tr>
<tr>
<td>4.</td>
<td>Achieve and maintain a healthy body weight by enjoying regular physical activity and healthy eating</td>
</tr>
<tr>
<td>5.</td>
<td>Limit salt, alcohol and caffeine</td>
</tr>
</tbody>
</table>

III.2.5 Food labeling, national nutrition monitoring, and recent developments

Food labeling

In March 1996 the Canadian Food Inspection Agency suggested the statement, “Consuming less cholesterol is one element of healthy eating” as an example of an acceptable message for food labeling (Canadian Food Inspection Agency, 1996). It was cautioned that Health Canada does not specify a cut-off for cholesterol intake and that reference to any recommended quantitative amount specified in guidelines from other countries is not acceptable.

The following health claim for food labels in Canada is permitted provided that the food contains 100 mg or less of cholesterol per 100 g of food, as well as adheres to some other conditions (Canadian Food Inspection Agency, 2004): “A healthy diet low in saturated and trans fats may reduce the risk of heart disease. (Naming the food) is low in saturated and trans fats.”

National nutrition monitoring and recent developments

National nutrition surveillance systems are considered valuable for contributing to public policy, program development, and monitoring of outcomes (Brulé, 2006). However, population-based food consumption data are collected only sporadically in Canada, and are often relatively out-of-date with sparse historical data available for comparison (Health Canada, 2000). The Nutrition Canada Survey conducted between 1970 and 1972 was the first and only comprehensive national nutrition survey (Kendall et al., 1997). Since that time, several provinces have conducted individual nutrition surveys or incorporated nutrition components into their other health surveys (Kendall et al., 1997). But, Canada still lacks a representative national dataset describing the food-based dietary practices of its citizens to inform the process of dietary guideline development (Anderson et al., 2003).

In other related developments, a new Canadian Academies of Science is being established to enhance the government, industry, and the public’s ability to access the best science on pressing issues to inform decisions, including matters of diet and health (Armstrong et al., 2005).
III.3 UNITED KINGDOM AND EUROPE

III.3.1 Overview

Rates of heart disease within the European Union (EU) show a north to south gradient, with the lowest rates in Mediterranean populations. Central and Eastern European countries have high rates of all cardiovascular diseases (Kafatos & Codington, 2000). Mortality rates from CHD have been declining in the United Kingdom since the late 1970s yet they continue to be the highest in Western Europe (British Heart Foundation, 2006). CHD is responsible for approximately 32% and 24% of premature deaths in U.K. men and women, respectively.

The Scientific Advisory Committee on Nutrition (SACN) advises the U.K. Food Standards Agency and the departments of health for England, Scotland, Northern Ireland, and Wales on scientific matters relating to food, diet and health (British Heart Foundation, 2006). The scope of topics covered by SACN includes the nutrient content of foods, dietary advice to achieve a balanced diet and prevent chronic diseases, and monitoring and surveillance of the nutrition status of U.K. populations, including vulnerable populations. The members appointed to SACN include independent scientific experts and consumer representatives. SACN met for the first time in June 2001 (UK Department of Health, 2001), replacing the Committee on Medical Aspects of Food Policy (COMA), which had served a similar role from 1963 until it was disbanded in March of 2000. The current chair of SACN was a member of COMA for ten years.

The United Kingdom is part of the EU. Therefore, U.K. laws regarding food labeling are based on EU legislation. Manufacturers selling products in the United Kingdom are not obligated by law to provide nutrition information, unless they make a nutrition claim. For those that do provide nutrition information, the energy value of the food and the amount of protein, carbohydrate and fat must be provided per 100 g or per 100 mL of food. Further information can be added voluntarily (provided no claim is made) on the amounts of other nutrients such as cholesterol (British Nutrition Foundation, 2006b).

III.3.2 European Heart Network and Eurodiet Working Party

EU dietary goals set average (mean) intake of populations for food policy purposes, and are not intended for individuals. Subpopulations such as infants and pregnant women are likely to have nutrition requirements that differ from the general population goals. The population approach attempts to shift the entire population toward lower risk behaviors and biomarkers, not just high-risk individuals.

James (2001) suggested that food-based dietary guidelines were best developed on a national basis rather than through pan-European mechanisms because the types of food consumed differ markedly across the continent. James reiterated a guiding principle of WHO/United Nations Food and Agricultural Organization (FAO), that dietary guidelines should be based on customary dietary patterns and take socioeconomic and cultural factors into account (Anonymous 2001a; 2001b).

Early Recommendation from the European Atherosclerosis Society

The Study Group of the European Atherosclerosis Society (1987) proposed strategies to reduce risk of CHD. None of its recommendations were accompanied by citations or supporting
evidence. The following recommendations were among those adopted for the general population, including high risk individuals:

- Decrease energy intake and increase exercise to control overweight
- Limit total fat intake to 30% or less of energy
- Limit saturated fat intake to less than 10% of energy
- Limit dietary cholesterol to less than 300 mg/d
- Increase intake of oleic acid and linoleic acid

European Heart Network and Eurodiet Working Party

The Eurodiet project, conducted from 1998 to 2000, was financed by the European Commission Directorate General for Health & Consumer Protection (Unit F/3) and the Ministry of Health Greece. Its dietary guidelines were presented in the Eurodiet core report, *Nutrition and Diet for Healthy Lifestyles in Europe* (Anonymous, 2001a; 2001b), and in the reports of the individual Eurodiet Working Parties (Kafatos & Codington, 2000). The Eurodiet population goals for fat are to consume less than 30% of energy as total fat to prevent obesity; saturated fat and *trans* fat are restricted to less than 10%, and 2% of energy, respectively, to reduce cardiovascular disease (Anonymous, 2001a).

The Eurodiet Working Party 1 (Luzzi, 2000) reviewed the recommendations of the International Task Force for the Prevention of Coronary Heart Disease (1998), which specified that dietary cholesterol should be maintained below 300 mg/d, or 200-250 mg/d for those needing further lowering of blood cholesterol concentration. No rationale was given by the task force for the selection of the specific cut-offs. The decision to reduce dietary cholesterol was based on experimental evidence that dietary cholesterol amplifies blood cholesterol and because some individuals have a heightened sensitivity to dietary cholesterol. In contrast to the task force, the Eurodiet Working Party 1 concluded that “in the European context, the specification for dietary cholesterol does not seem to be of practical significance as the intakes in Europe are on average well within this limit” (Kafatos & Codington, 2000). Thus, following the conclusions of experts involved in Working Party 1, the Eurodiet core report did not mention dietary cholesterol (Kafatos & Codington, 2000).

The Brussels-based European Heart Network (EHN) is an alliance of national heart-health foundations and organizations from 26 countries, many of which are not members of the EU. Among the EHN’s latest population goals for intake, total fat is restricted to 30% of energy to prevent obesity and saturated fat and *trans* fat are restricted to less than 10%, and 2% of energy, respectively, to reduce cardiovascular disease (European Heart Network, 2002). As of this writing, no EU member state has met the EHN population goal for saturated fat intake. These goals were based on evidence compiled by the Eurodiet project, and reflect EHN’s agreement with Eurodiet goals. The following paragraph summarizes the review of evidence leading to the decision by EHN (2002) to omit a specific goal for dietary cholesterol:

Cholesterol in the diet increases LDL-cholesterol levels in the blood, but to a much lesser extent than saturated fat, and the response varies widely among individuals. Foods high in cholesterol are usually also high in saturated fat, so that reducing intakes of saturated fat, as described previously, should lead to an accompanying fall in cholesterol intakes. Although there is some evidence of a relationship between cholesterol consumption and cardiovascular disease (Weggemans *et al*., 2001), no population goal is included because
dietary cholesterol intakes in Europe tend to be within the usual population goal of less than 300 mg per day specified by expert groups and consensus documents.

### III.3.3 U.K. diet and health reports and recent recommendations

During the 1990s, COMA recommended population goals (not individual targets) of no more than 35% of food energy as fat, no more than 11% of food energy intake as saturated fat, and recommended that the average intake of dietary cholesterol should not rise. At that time, total fat in the U.K. diet provided about 40% of energy, saturated fat about 16% of energy and dietary cholesterol was approximately 245 mg/d (British Nutrition Foundation, 2006a; Jackson, 2001). The 1992 National Food Survey indicated that each individual in the average household was consuming two eggs per week (Stockley & Health Education Authority, 1996).

The most recent dietary recommendations of the Department of Health, London, *Choosing a Better Diet: a Food and Health Action Plan* (2005), do not mention cholesterol. The objectives include reducing the average intake of saturated fat to 11% of food energy (currently 13.3%) and maintaining the trend toward lower average total fat intake to meet 35% of food energy (currently 35.3%).

Dietary education materials of the Food Standards Agency and other U.K. government agencies either do not mention cholesterol (UK Department of Health & UK Department for Education and Skills, 2006; UK Food Standards Agency, 2005b) or if dietary cholesterol is mentioned, the dietary advice focuses on reducing saturated fats (UK Food Standards Agency, 2005a). Diet and health reports published by prominent U.K. public and medical groups are listed in Table III-6.
Table III-6. A selection of U.K. publications addressing diet and cardiovascular disease


III.3.4 British Egg Information Service

On August 16, 2001, the British Egg Information Service (BEIS) of the British Egg Industry Council wrote to the SACN Secretariat requesting that SACN consider and update past government advice in relation to dietary cholesterol, egg intake and cardiovascular disease (Appendix E) (Cryer, 2001a; 2001b). The official advice at that time was the long-standing 1994 COMA report *Nutritional Aspects of Cardiovascular Disease*, which suggested that average cholesterol intake should not increase. Consumer research conducted by BEIS suggested that the public believed that egg intake should be limited to two per week (Cryer, 2001a; 2001b).

To support its request, BEIS cited Hu *et al.* (1999) and Howell *et al.* (1997) as suggesting that dietary cholesterol does not significantly affect the ratio of LDL-cholesterol and HDL-cholesterol, a biomarker for cardiovascular disease. Hu *et al.* (1999) analyzed results of the Health Professional Follow-up Study and the Nurses’ Health Study conducted in the United States, from which they estimated that egg consumption contributed to 32% of total dietary cholesterol during the study period from 1980 to 1994. Hu *et al.* (1999) did not report blood cholesterol levels, but did suppose it conceivable “that the small adverse effect of cholesterol in an egg on plasma LDL levels is counterbalanced by potential beneficial effects on HDL and triglycerides, and of other nutrients including antioxidants, folate, other B vitamins, and unsaturated fats.” Howell *et al.* (1997) conducted a meta-analysis of 224 studies, some of which measured LDL-cholesterol and/or HDL-cholesterol. The meta-analysis suggested to Howell *et al.* (1997) that blood LDL-cholesterol concentrations were determined by intake of saturated fat and polyunsaturated fats and blood HDL-cholesterol concentrations were determined by changes in saturated fat and total fat. Howell *et al.* (1997) suggested that dietary cholesterol has a relatively modest effect on blood cholesterol in most patients who are diet-sensitive, amounting to approximately a 1% decline in the population average total blood cholesterol concentration if dietary cholesterol were decreased by 100 mg/d. Howell *et al.* (1997) predicted a 5% decline in blood total and LDL-cholesterol overall if diets complied with recommendations for 30% energy from fat, less than 10% energy as saturated fat, and less than 300 mg/d of dietary cholesterol.

According to SACN (Jackson, 2001), BEIS also pointed to the then-recently-revised recommendations of AHA to build its case further, claiming that AHA acknowledged that individuals can eat an egg a day if the total cholesterol in their diet is limited. AHA did not in fact set specific levels of egg intake. It set a limit for the general population of 300 mg/d of cholesterol and even lower intake limits for individuals with high risk of cardiovascular disease based on blood lipid concentrations and other clinical parameters. AHA stated that its recommendations could be readily achieved, even with “periodic consumption” of eggs and shellfish (Krauss *et al.*, 2000).

SACN considered the evidence presented by BEIS (including AHA recommendations) as well as other recent reviews, only one of which was identified (Weggemans *et al.*, 2001). After discussion with the Chairman of SACN, the Secretariat responded to BEIS in November, 2001 (Appendix E), clarifying that COMA did not prescribe a limit on egg consumption, but that its recommendations take into account dietary cholesterol from all sources. The Secretariat mentioned that several studies had shown dietary cholesterol to increase both LDL-cholesterol and HDL-cholesterol but cited only the meta-analysis of Weggemans *et al.* (2001). The Secretariat also cited Weggemans *et al.* (2001) as indicating that dietary cholesterol raises the ratio of total to HDL-cholesterol in humans, adversely effecting the cholesterol profile.
Weggemans et al. (2001) reviewed 17 crossover or controlled parallel-design studies reporting cholesterol intake and blood HDL-cholesterol concentrations. Eleven of these studies were conducted in a metabolic ward, but only seven studies included female subjects. The change in dietary cholesterol among healthy, diabetic, and hyperlipidemic subjects ranged from 137 to 897 mg/d. Because only six studies reported the average ratios of total to HDL-cholesterol, Weggemans et al. (2001) calculated mean ratios for the remainder studies using group mean values for blood total cholesterol and HDL-cholesterol. From these data they predicted that a 100 mg/d increase in dietary cholesterol would lead to a change of 0.020±0.005 units (mean±SEE) in the total:HDL-cholesterol ratio. Weggemans et al. (2001) suggested that the clinical significance of this effect on raising the risk for CHD may not be significant for an individual, but may have substantial clinical relevance at the population level.

According to the Secretariat (Jackson, 2001), because the ratio of total to HDL-cholesterol involves the opposing effects of LDL-cholesterol and HDL-cholesterol, this ratio is a better predictor of CHD risk than are individual lipoprotein concentrations (not referenced). Consequently, the Secretariat decided that the 1994 COMA recommendation “that average dietary intake of cholesterol should not rise” is still valid. At its December 2001 meeting, members of SACN (2001) agreed with the Secretariat’s response to BEIS.

In June 2002, SACN discussed revised recommendations made by the Subgroup on Risk Assessment for the types of evidence that SACN should consider when evaluating the relationship between food, nutrients, and health. SACN (2006; 2001) recommended that in the future, evidence should be presented in a systematic and transparent way, allowing judgments to be made on both the quantitative and qualitative aspects of the included studies. Such future reviews should cover the appropriateness of statistical methods, confounding factors, and the consistency of meta-analysis results. SACN noted that it would also take into account any existing U.K. public health policies for any issue under review.

III.3.5 Diet and health surveys

Monitoring and surveillance activities in Great Britain (England, Scotland, and Wales) have helped to inform experts about trends in biomarkers of CHD and whether the public is complying with dietary recommendations.

Health Survey for England

The Health Survey for England comprises a series of annual surveys designed to provide a representative sample of the population living in private households in England. The surveys are carried out by the Joint Health Surveys Unit of the National Centre for Social Research and the Department of Epidemiology and Public Health at the Royal Free and University College Medical School, and consist of an interview and a home visit by a nurse.

For the 2003 survey, interviews were held in 8,867 households with 18,553 individuals. Mean blood total cholesterol was 5.5 mmol/L (213 mg/dL) in men and 5.6 mmol/L (217 mg/dL) in women, with 66% of men and women having an elevated total cholesterol level of 5.0 mmol/L (193 mg/dL) or greater. LDL-cholesterol averaged 3.6±SEM0.5 mmol/L (139±SEM1.9 mg/dL) for both men (n=332) and women (n=429), 77% and 74% of whom, respectively, had levels above 3.0 mmol/L (116 mg/dL). There were no significant changes in mean blood total cholesterol concentrations from the 2002 survey.
cholesterol concentration between 1998 and 2003. However, the prevalence of elevated blood total cholesterol was greater in 2003 than in 1998 (UK Department of Health, 2003).

**National Diet and Nutrition Survey in Great Britain**

The *National Diet and Nutrition Survey* (NDNS) is conducted in Great Britain and is used by the government to develop policy. A summary of the survey data from volumes one through four was published in 2004. According to summary data, 67% of men and 52% of women participating in the NDNS were obese and/or overweight (British Nutrition Foundation, 2005).

Data on fat intake recorded from NDNS respondents who kept a full 7-day diary record (n=1,724) was published in volume two (Henderson *et al.*, 2003). From July 2000 through June 2001, the average daily total fat intake for men (87 g) represented 36% of food energy, and the average total fat intake for women (61g) represented 35% of food energy. Fat intake represented a substantially lower proportion of energy than in the 1986/87 survey. On average, women (but not men) were compliant with the COMA-recommended upper limit for dietary fat of 35% of food energy. The survey also showed that saturated fat provided 13% of food energy for both men and women, which exceeded the COMA-recommended 11% (British Nutrition Foundation, 2006a). The average cholesterol intake was 304±SD128 mg/d for men and 213±95mg/d for women (Henderson *et al.*, 2003). Men 35 years of age and older had average dietary cholesterol intakes greater than 300 mg/d and median intakes just under 300 mg/d (Henderson *et al.*, 2003).

**III.3.6 Efforts in Scotland**

The Scottish Executive Health Department and the Food Standards Agency Scotland share responsibility for national nutrition policy. In 1996, the Scottish Office published *Eating for Health. A Diet Action Plan for Scotland* (SDAP) (The Scottish Office, 1996), which was eventually endorsed by the Scottish Parliament (The Scottish Office, 2000). SDAP set out national targets, which included improving diet and physical activity by tackling inequalities through social and economic policy and other means. Various steps that stakeholders from agriculture, the retail sector, public health and consumer interest groups could undertake on a voluntary basis to improve the Scottish diet were discussed. The timeline for achievement projected that many goals would be completed by 2005. Because of the strong cultural attachment to foods rich in fat, salt, and sugar, reducing intake of such foods was considered long-term goals. This effort was further documented in the white paper *Towards a Healthier Scotland* (The Scottish Office, 1999).

In 2003, a wider strategic framework for action was laid out in the Scottish Executive's paper *Improving Health in Scotland - The Challenge* (The Scottish Office, 2003). The primary dietary goals in this document were to increase fruit and vegetable intake by mid-2004 and to reach a 2005 target of an average intake of more than 400 grams *per day*. The fat-related Scottish dietary targets for 2005 were that average intake of total fat would reduce from 40.7% to no more than 35% of food energy and that average intake of saturated fatty acids would be reduced from 16.6% to no more than 11% of food energy (The Scottish Office, 2005b). Dietary cholesterol is not currently included as a goal or target for monitoring.

A Working Group on Monitoring Scottish Dietary Targets was established in April 2003 to investigate and report ways of assessing progress made toward the Scottish dietary targets and to advise on surveillance requirements beyond 2005. The Working Group’s main recommendations...
were that progress could be monitored by data collected in the Expenditure and Food Surveys, supplemented with data from enhanced modules in the Scottish Health Surveys and National Diet and Nutrition Surveys (The Scottish Office, 2005a). One suggested enhancement was to replace the existing eating habits module of the Scottish Health Survey with a comprehensive food frequency questionnaire. Another suggestion was to include measures of total fat intake in future monitoring tools.

### III.4 WORLD HEALTH ORGANIZATION

WHO attributes one-third of all annual global deaths (15.3 million) to cardiovascular disease. The WHO Study Group on Diet, Nutrition and Prevention of Noncommunicable Diseases advocates a population approach to reduce national mortality rates for chronic diseases. In contrast to recommendations aimed at individuals, population nutrient intake goals target national food security and equity of food distribution. Such an approach aims to influence governmental policy to enact favorable changes in food production and supply, thereby enhancing the options for healthy food choices by individuals.

#### III.4.1 Early efforts

The WHO Technical Report Series of documents on diet and health are prepared from proceedings of meetings of Joint WHO/FAO Expert Consultation. These reports contain the collective views of an international group of experts, who meet over a period of days. The Expert Consultation often obtains its substantive materials from background papers prepared by academic and public health experts and may take into consideration invited commentary from additional experts. The process for how experts are selected is not transparent (Burman, 2002).

In 1990, the eleven member WHO Study Group on Diet, Nutrition and Prevention of Noncommunicable Diseases set goal limits for population average intake of cholesterol of between zero and an upper limit of 300 mg/d to prevent chronic diseases (World Health Organization, 1991). That report, *Diet, Nutrition and the Prevention of Chronic Diseases. Technical Report Series, No. 797* served as a reference for the *World Declaration and Plan of Action for Nutrition* adopted at the December 1992 International Conference on Nutrition. These actions were highly influential. As of 1993, 94 countries and 6 territories had developed or revised national dietary guidelines, many in the form of food-based dietary guidelines (Nishida et al., 2004).

WHO/FAO recognized that unhealthy lifestyles and diets were associated with raised blood pressure, impaired glucose tolerance, and dyslipidemia in children and adolescents. The evidence reviewed by WHO/FAO (2002) of a role for dietary cholesterol in abnormal clinical conditions in children came from findings in the Bogalusa Heart Study (Nicklas et al., 1988) and from the Cardiovascular Risk in Young Finns study, which associated the preference for butter over margarine with higher blood LDL-cholesterol (Raitakari et al., 1994). In the Bogalusa Heart Study, dietary intake and blood lipoproteins were measured in children in Bogalusa, Louisiana, at age 6 months, yearly through age 4, and finally at age 7. Among the 50 children who participated in all six screenings, those in the upper tertile of cholesterol intake (mg/1000 kcal) at 7 years of age had average levels of blood LDL-cholesterol that were approximately 14 mg/dL higher than children in the remaining tertiles (Nicklas et al., 1988). In the Cardiovascular Risk in Young Finns study, venous blood samples were taken from adolescents (n=1398; 15 to 24 years of age) after an overnight fast (Raitakari et al., 1994). Boys and girls who used butter on
bread had 0.26 mmol/L (10 mg/dL) and 0.19 mmol/L (7.4 mg/dL) higher ($P < 0.01$) concentrations of LDL-cholesterol, respectively, than those who did not.

WHO/FAO (2003) considered that high intake of dietary cholesterol has been confirmed to lead to an increased risk for CHD. It cited reviews by Hooper et al. (2001b; 2001a) and a study by Hu et al. (2000) to support this conclusion. Hooper et al. conducted a systematic review of randomized clinical trials to assess the effect of reducing dietary fat on cardiovascular morbidity and mortality over at least 6 months. The pooled results indicated that general reduction of dietary fat significantly reduced the incidence of combined cardiovascular events by 16% and cardiovascular deaths by 9%, yet the effect on total mortality was not significant. The specific role played by dietary cholesterol, if any, was not elucidated.

The study by Hu et al. (2000) consisted of scoring baseline intakes of 44,875 men, collected by food frequency questionnaire. Each individual’s diet was scored twice, once for its similarity with a “prudent” diet (characterized by intake of fruits, vegetables, fish, and poultry) and again for its similarity to a “Western” diet (characterized by red meat, fast foods, high-fat dairy products, and refined carbohydrates). The resulting scores for each diet type (prudent or Western) were divided into quintiles from lowest to highest, with highest reflecting diets as a whole that came closest to best characterizing the diet category. Diets best characterizing the Western diet had cholesterol intake (mean±SD) of 335±126 mg/d compared with 288±107 mg/d for those diets best characterizing the prudent diet (Hu et al., 2000). The men were then followed until the occurrence of myocardial infarction, death, or for eight years through January 1994. After adjustment for age and CHD risk factors, a trend for decreasing relative risk of CHD was evident from lowest to highest quintiles of the prudent diet ($P < 0.001$). In contrast, a trend for increasing relative risk was evident across quintiles of the Western diet, from lowest to highest quintile ($P < 0.0001$). This study indicated that Western-type diets were more likely to lead to CHD than prudent-type diets.

To reduce the risk of cardiovascular disease, WHO/FAO (2003) continued to recommend an average per capita intake of less than 300 mg/d cholesterol. WHO/FAO further advised that cholesterol intake should be as low as possible, but that severely restricting intake of egg yolks was unnecessary if dairy fat and meat intake were controlled. The strength of the evidence that dietary cholesterol increased the risk of developing cardiovascular diseases was summarized as “probable” rather than as “insufficient,” “possible,” or “convincing.” WHO/FAO (2003) did not provide a rationale for limiting the population intake of dietary cholesterol to less than 300 mg/d versus some other cut-off. WHO/FAO cited the Nutrition Committee of AHA to support its advice that cholesterol intake be kept as low as possible. In that report, Kris-Etherton et al. (2001) mentioned that current dietary guidance for individuals was less than 300 mg/d.

### III.4.2 Recent strategy

Recognizing the need to reduce the level of exposure to the major risks resulting from unhealthy diet and physical inactivity and the largely preventable nature of the consequent diseases, WHO planned to develop a global strategy for diet, physical activity, and health. It distributed the report of a Joint WHO/FAO Expert Consultation, *Diet, Nutrition and the Prevention of Chronic Diseases*, to its members in March 2003, along with a discussion paper for them to consider (World Health Organization, 2003). Six regional consultations involving more than 80 countries were held by June 2003. Additional consultations were held with other organizations of the United Nations system (*e.g.*, the World Bank) and with 137 civil society organizations from 49...
countries. Discussions with individual businesses and industry associations included a round-
table discussion with senior executives from major food and sports-related companies. These
efforts and communications led WHO/FAO to draft a global strategy for diet, physical activity,
and health, which was endorsed by the 57th World Health Assembly of WHO (2004).

WHO (2004) recommended that both populations and individuals “limit energy intake from total
fats and shift fat consumption away from saturated fats to unsaturated fats and towards the
elimination of trans-fatty acids,” but this latest report did not make any recommendations for
dietary cholesterol.
IV. SUMMARY OF EVIDENCE AND APPROACHES LEADING TO PRINCIPAL RECOMMENDATIONS

In recent years, the various expert committees assembled to develop dietary recommendations for cholesterol intake have primarily used formal methods of analysis of scientific evidence along with expert opinion. Technical reports resulting from these efforts have informed federal regulators responsible for establishing or updating national dietary guidelines. Typically, proposed guidelines are not finalized until comments submitted by the public, industry, and other stakeholders are also considered. Technical supporting materials tend to be made publicly available along with the consumer-oriented guidance documents, and often, but not always, these documents describe the process leading to the dietary guideline and cite the evidence upon which the guideline was based. Table IV-1 summarizes the composition of expert committees that have advised federal regulators, the sources of principal evidence, whether the evidence was rated according to a formal system, whether the public was afforded an opportunity to provide comment prior to guideline completion, and the main conclusions for the countries included in this report.

Among the current national and international guidelines reviewed in this report, all agree on the necessity to reduce saturated fat but dietary guidelines in the United States are the only ones that also recommend a quantitative threshold for cholesterol intake. The complexity of constructing national guidelines for dietary intake may contribute to differences in recommendations between nations, particularly the acceptability of foods and the psychological, social, and cultural issues that affect food preference (Cooper & Zlotkin, 2003).

In practical terms, the United States has food product labels specifying a Daily Value of, at most, 300 mg (in place since 1995), and any change in U.S. guidelines for cholesterol intake would have to coordinate these messages. In the minds of U.S. regulators and of the expert panels that inform them, scientific evidence to date has not justified replacing or omitting the 300 mg/d cut-off for the general public. In fact, based on U.S. clinical guidelines, the U.S. dietary guidelines now recommend an even more stringent limit of 200 mg/d for those with elevated blood low density lipoprotein (LDL)-cholesterol.

Given the differences in time when recommendations for Australia, Canada, and the United Kingdom were last issued (1992 through 2005), it appears that accumulating data on the relationship between diet and cardiovascular health have failed to reach a significance that would prompt these countries to recommend restricting dietary cholesterol as a primary public health strategy to lower blood cholesterol.

Regulators in the United States and Canada rely upon the Institute of Medicine (IOM) reports for comprehensive and up-to-date reviews of the scientific evidence for the relationship between dietary cholesterol and chronic disease to inform their decisions in setting national dietary guidelines for cholesterol intake. It will be interesting to see whether the IOM’s (2005b) inability to quantify a no-observed-adverse-effect level for cholesterol intake will influence the new Canadian dietary guidelines, which are due out within the next six months. Preliminary food modeling exercises conducted by the U.S. Department of Agriculture (USDA) suggest that healthy food patterns for lacto-ovo vegetarians contain approximately 160 to 212 mg/d of cholesterol, depending on energy requirements, helping to define what “low” intakes might be possible (U.S. Department of Agriculture, 2005c). The next issue of the U.S. dietary guidelines is planned for 2010.
Next steps

Fortunately, blood lipid concentrations have been declining in the United States rather substantially and there has been a decline in coronary heart disease (CHD) in the United States and other countries as well. The amount and types of dietary fats influence the development of atherosclerosis and CHD yet questions remain as to the most heart-healthy mix of dietary fats for the general population. Continuing research on the health benefits and risks of different types of fat and food ingredients may provide support for new consumer messages and trickle-down effects in industry that will deliver greater health benefits than do the current dietary guidelines. For example, can it be determined which saturated fats are most atherosclerotic and can these be decreased in the food supply? How will increasing polyunsaturated fatty acids, especially omega-3 fatty acids either from vegetables or from fish, alter the risk of CHD?

Dietary guidelines must be based on the average population, presuming varying susceptibilities within the population. IOM determined that more information is needed on the contributing factors in individual variation of LDL-cholesterol response to dietary cholesterol (i.e., genetic variants and non-cholesterol components of diet). The reports of the INTERLIPID (Ueshima et al., 2003) and INTERMAP (Zhou et al., 2003) studies are raising interesting hypotheses regarding eating patterns and very high consumption of cholesterol in the diet among Japanese in Japan compared with samples in the United States or the United Kingdom. The Japanese diet is typically high in cholesterol (446 mg/d among men and 359 mg/d among women) and omega-3 fatty acid, yet is lower in total fat and in saturated fat than diets in Western industrialized countries (Ueshima et al., 2003; Zhou et al., 2003). This population has relatively low body weight, relatively lower LDL-cholesterol and lower risk of CHD comparable to the U.S. and U.K. populations but higher risk of stroke (Ueshima et al., 2003; Viikari et al., 2004; Wang et al., 2005; Wennlof et al., 2005; Zhou et al., 2003).

Overall, the majority of studies on the health aspects of dietary cholesterol and blood cholesterol are of adults. Further research is needed to better define optimal blood cholesterol concentrations and other cardiovascular risk factors for healthy children, particularly with regard to biological age (pubertal status) and sex-related differences (Ong et al., 2006). Further research is needed to determine the optimal dietary fat composition during childhood to minimize long-term risk for CHD while supporting healthy growth and development (Barter et al., 2006). Such studies will inform school feeding programs and other public health activities and are especially important given the rise in pediatric obesity and pediatric type II diabetes, which increase risk of cardiovascular diseases. In 1999-2000, peak intake of 375 mg/d of cholesterol in boys was reached between 16 to 19 years of age. Among males age 12 to 19 years, the mean (but not median) cholesterol intake exceeded 300 mg/d regardless of racial/ethnic group. Should targeted efforts be undertaken to reduce the intake of dietary cholesterol in these groups and to better understand the quantitative relationship between lowering dietary cholesterol or saturated fat intake and blood total or LDL-cholesterol in adolescence?

Research that explores the effects of very small incremental changes in dietary cholesterol to define the lowest level of cholesterol intake shown to increase total or LDL-cholesterol concentration might be beneficial for defining a threshold for cholesterol intake. To complement these efforts, further food modeling studies by USDA could provide information that might assist in creating sample healthy food patterns and planning nutritious diets containing “low” amounts of dietary cholesterol.
Finally, dietary guidelines should remain evidence-based and be modified consistent with advances in science, particularly as our understanding of the mechanisms of pathogenesis of CHD improves and new biomarkers of disease are identified. A direct assessment of the validity of the cholesterol dietary guidance documents is needed to determine whether recommended levels of cholesterol intake result in reduced levels of the biomarkers of disease (i.e., LDL-cholesterol) and contribute to reductions in CHD. Barter et al. (2006) proposed that measures of apolipoprotein B (apo B) are more informative than LDL-cholesterol as an index of the risk of cardiovascular events:

There is abundant evidence that the risk of atherosclerotic vascular disease is directly related to plasma cholesterol levels. Accordingly, all of the national and transnational screening and therapeutic guidelines are based on total or LDL cholesterol. This presumes that cholesterol is the most important lipoprotein-related proatherogenic risk variable. On the contrary, risk appears to be more directly related to the number of circulating atherogenic particles that contact and enter the arterial wall than to the measured concentration of cholesterol in these lipoprotein fractions. Each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein (apo) B and therefore the concentration of apo B provides a direct measure of the number of circulating atherogenic lipoproteins. Evidence from fundamental, epidemiological and clinical trial studies indicates that apo B is superior to any of the cholesterol indices to recognize those at increased risk of vascular disease and to judge the adequacy of lipid-lowering therapy.

If a change takes hold to adopt apo B and the apo B/apo A-I ratio as biomarkers for CHD risk, it will propel us to question what dietary factors, if any, influence them and what related dietary modifications might minimize the risk of cardiovascular disease.
Table IV-1. Summary of current authoritative guidelines for dietary cholesterol and aspects of the process leading to key findings

<table>
<thead>
<tr>
<th>Authoritative Source</th>
<th>Expert Committee</th>
<th>Source of Data</th>
<th>Rating of evidence</th>
<th>Key Conclusion</th>
<th>Public input</th>
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<tr>
<td><strong>Australia</strong></td>
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<tr>
<td><em>Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes (National Health and Medical Research Council, 2006a)</em></td>
<td>Work group of public health and nutrition experts, consumer and industry representatives, and federal regulators</td>
<td>Evidence-based assessment of key papers used in U.S./Canadian DRI(^1) for cholesterol (National Health and Medical Research Council, 2003a), guidelines of other key countries and WHO, dietary survey data, and other data published more recently or missing from other reviews that was identified by the reviewer as relevant</td>
<td>Level of evidence rated by FSANZ system</td>
<td>Dietary cholesterol is not essential and this finding is in agreement with IOM</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Dietary Guidelines for Children and Adolescents in Australia</em> (National Health and Medical Research Council, 2003a)</td>
<td>Federal and academic health and nutrition science experts, consumer representative, assembled as a Working Party; One reviewer prepared the technical document of adult fat intake guidelines and another prepared the pediatric fat intake guidelines</td>
<td>Food-based guidelines developed via predetermined processes of evidence-based development, consultation, review, and independent assessment. Assess the evidence of the efficacy of fat and cholesterol in relation to specific health outcomes. Included reviews, several controlled experiments, meta-analyses, position statements on dietary fats, autopsy studies of coronary atherosclerosis in children</td>
<td>Level of evidence rated by FSANZ system</td>
<td>The cholesterol-elevating effect of dietary cholesterol is less consistent than that of saturated fats. Overly limiting fat and cholesterol intake has led to growth failure of children. Advice to reduce saturated fat will bring with it lower cholesterol intake since these two lipid classes usually occur in the same foods</td>
<td>Yes</td>
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### Authoritative Source

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<tr>
<td><strong>Canada</strong></td>
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<tr>
<td><strong>Dietary Reference Intakes (Institute of Medicine, 2005b)^2</strong></td>
<td>(See U.S. source)</td>
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<td><strong>Canada's Food Guide to Healthy Eating (1992), (Health Canada, 1997a); Canada's Guidelines for Healthy Eating (Health Canada, 2002b)</strong></td>
<td>For 1992, the Communications and Implementation Committee translated recommendations by the Scientific Review Committee (1990), whose member names (but not affiliations) were identified. For the 2006/2007 revision, Health Canada is working with an external Food Guide Advisory Committee, an Interdepartmental Working Group, and a DRI Committee</td>
<td>The current (1992) document was based on Nutrition Recommendations (1990) of the Scientific Review Committee, whose cholesterol chapter was reviewed by two external reviewers. Specific supporting evidence was neither cited nor discussed in the current (1992) document nor the accompanying background document for educators and communicators. The 2006/2007 revision will be based on the DRI report, food purchasing patterns, the demographic characteristics in Canada, and reports summarizing the evidence on the relationships between select foods and their potential effect on prevention of chronic disease</td>
<td>In 1992, evidence was not rated</td>
<td>Dietary cholesterol is not the main influence on blood cholesterol level, although it has some effect, in some people. The key dietary strategy for controlling blood cholesterol is to reduce the intake of total fat and, specifically, saturated fat (1992)</td>
<td>Yes for 2006/2007</td>
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<td><strong>United Kingdom</strong></td>
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<td><strong>Letter of the Secretariat of SACN (Jackson, 2001)</strong></td>
<td>The Secretariat of SACN; Secretariat’s findings were endorsed by committee</td>
<td>AHA recommendations and recent published reviews, only one of which was identified (2005)</td>
<td>No</td>
<td>1994 Committee on Medical Aspects of Food Policy recommendation “that average dietary intake of cholesterol should not rise” is still valid</td>
<td>No</td>
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Table IV-1. Summary of current authoritative guidelines for dietary cholesterol and aspects of the process leading to key findings

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<td><em>Choosing Health</em> (2004)</td>
<td>Department of Health Ministers</td>
<td>Consultative process involving more than 200 stakeholders</td>
<td>No</td>
<td>Objectives focus on reducing saturated fats and lowering the average total fat intake; cholesterol is not discussed</td>
<td>Yes</td>
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| **United States** | | | | |
| *Dietary Reference Intakes* (Institute of Medicine, 2005b) | Macronutrient Panel of academic and medical experts in nutrition and collaborating DRI committees, e.g., the Subcommittee on Upper Reference Levels of Nutrients composed of experts in toxicology | Data were obtained to conduct a risk assessment (identify a related serious adverse effect, derive a Tolerable Upper Intake Level, determine the fraction of the population with intakes above a Tolerable Upper Intake Level). Published data were reanalyzed to generate regression models for the relationships between change in diet (by type) and change in blood cholesterol | Evidence was not rated but categories of evidence (preclinical, epidemiology, clinical) were characterized | “there is no evidence for a biological requirement for dietary cholesterol” “any incremental increase in cholesterol intake increases CHD risk” A Tolerable Upper Intake Level could not be set | Yes |

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<tr>
<td><em>Dietary Guidelines for Americans</em> (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2005)</td>
<td>Medical and academic experts in diet and health selected by the Secretaries of DHHS and USDA</td>
<td>Reviewed the 2000 guidelines (Institute of Medicine, 2005b). Relied on findings in <em>Dietary Reference Intakes</em> (Franz et al., 2004; National Heart, Lung, and Blood Institute, 2002), clinical guidelines (National Heart, Lung, and Blood Institute, 2002), and conducted food modeling exercises. It also reviewed five additional trials, which it did not identify</td>
<td>Evidence not rated; however, at least one of the reports reviewed included rated evidence (Expert Panel on Detection, Evaluation and Treatment of High blood Cholesterol in Adults, 2001)</td>
<td>Retain guideline at maximum of 300 mg/d for adults with an LDL-cholesterol below 130 mg/dL; For adults with an LDL-cholesterol of 130 mg/dL or higher, less than 200 mg/d of dietary cholesterol is recommended (the cholesterol recommendation accompanies a recommendation to consume less than 10% of calories as saturated fat). Increases in blood cholesterol are expected to progressively increase the risk of CHD. Because dietary cholesterol can raise blood LDL-cholesterol, higher intakes of dietary cholesterol could raise the risk of CHD. Reducing cholesterol intakes from high to low could decrease blood LDL-cholesterol and decrease the risk of CHD in most persons</td>
<td>Yes</td>
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2. IOM DRI developed in unison with Canada and United States.

3. As specified by the provisions of the Nutrition Labeling and Education Act of 1990, such as 101.9 (c), the percentage of the “Daily Value” of cholesterol provided by a food is determined from the Daily Reference Value that the FDA established for macronutrients (fats).
V. LITERATURE CITATIONS


LSRO Report: Approach to Establish Guidelines for Cholesterol Intake


LSRO Report: Approach to Establish Guidelines for Cholesterol Intake


LSRO Report: Approach to Establish Guidelines for Cholesterol Intake


VI. STUDY PARTICIPANTS

VI.1 AD HOC EXPERT REVIEWERS

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Director Emeritus, American Society for Nutrition
Bethesda, MD

Lewis Kuller, M.D., Dr.P.H.
University Professor of Public Health
Professor of Epidemiology
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, PA

VI.2 LIFE SCIENCES RESEARCH OFFICE STAFF

Michael Falk, Ph.D.
Executive Director

Catherine J. Klein, Ph.D., R.D., C.N.S.D.
Senior Staff Scientist

Karin French, B.S.
Associate Staff Scientist

Robin S. Feldman, B.S., M.B.A.
Literature Specialist Librarian

Rebecca Lynn Johnson, Ph.D.
Assistant Information Specialist
APPENDIX A. INDIVIDUALS AND ORGANIZATIONS

A.1 BIOGRAPHICAL SUMMARIES OF AD HOC EXPERT REVIEWERS

Richard G. Allison, Ph.D. is a Senior Scientific Advisor to the Life Sciences Research Office. He was Science Officer and Executive Director of the American Society for Nutrition (ASN) since 1984. Prior to this, he was a Senior Staff Scientist with the Federation of American Societies for Experimental Biology LSRO. Dr. Allison earned a B.S. in biochemistry at the Pennsylvania State University, University Park, PA and a Ph.D. in nutrition at the University of California, Davis, CA. Dr. Allison’s primary research interests have been in the area of protein chemistry and he has authored numerous papers for the Human Nutrition Information Service, (U.S. Department of Agriculture) and the Bureau of Foods, (U.S. Food and Drug Administration; FDA) on a variety of food and nutrition-related topics. He was honored by the FDA Commissioner’s Special Citation in recognition of outstanding scientific contributions to public health in human nutrition and safety of food substances as food ingredients Generally Recognized As Safe. In addition to ASN, Dr. Allison is a member of the Council of Engineering and Scientific Society Executives and the Institute of Food Technologists.

Lewis Kuller, M.D., Dr.P.H. is a University Professor of Public Health at the University of Pittsburgh. He received a B.S. from Hamilton College, Clinton, NY, earned a M.D. from George Washington University Medical School, Washington, DC and a M.S. and Ph.D. in public health from Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MD. He is past Chair of the Department of Epidemiology (1972-2002), University of Pittsburgh Graduate School of Public Health. Dr. Kuller is a former member of the National Advisory Council on Aging at the National Institute on Aging, from 2001-2005, and currently serves on the National Cholesterol Education Program. He is board-certified in preventive medicine and is a Fellow of the American College of Cardiology, the American College of Preventive Medicine, and the American Epidemiological Society. Dr. Kuller has published over 500 papers in cardiovascular diseases, women’s health, aging, diabetes, and cancer. He has been the recipient of the following awards/honors: Distinguished Achievement Award from the American Heart Association, the Chancellor's Distinguished Research Award (University of Pittsburgh), the Johns Hopkins University Society of Scholars, the Abraham Lilienfeld Award (American College of Epidemiology), and an Alumni Achievement Award (George Washington University).

A.2 BIOGRAPHICAL SUMMARIES OF LIFE SCIENCES RESEARCH OFFICE STAFF

Michael Falk, Ph.D., is the Director of the Life Sciences Research Office Inc. (LSRO). He received his Ph.D. in biochemistry from Cornell University and completed postdoctoral training at Harvard Medical School. He was employed in various capacities at the Naval Medical Research Institute, Bethesda, MD supervising as many as 80 senior level scientists. As Principal Investigator he was a key member of the Scientific Advisory Board and Acting Director for the institute. He was also the Director of the Wound Repair Program and Director of Biochemistry and Cell Biology. As Director, he rescued the Septic Shock Research Program by cutting inefficiencies and increasing productivity in terms of grant funding and publication production. He managed peer reviews and subject review panels in infectious diseases, environmental sciences, military medicine, and other health-related fields for the National Science Foundation, the Medical Research Council of Canada, and the Office of Naval Research. As Director of LSRO, Dr. Falk manages the evaluation of biomedical information and scientific opinion for regulatory and policy makers in both the public and private sectors. He has written seminal
white papers on infant nutrition, food labeling, food safety, and military dental research, and has organized two international conferences.

Robin S. Feldman, B.S., M.B.A., is the Literature Specialist at LSRO. She is an information specialist with experience in the electronic acquisition, analysis, and management of scientific, business, and regulatory information. Ms. Feldman obtained her B.S. from George Washington University, Washington, D.C., with a major in zoology and an M.B.A. with a concentration in science and technology from the University of Maryland at College Park. Previously, she worked as Biomedical Research Assistant at Consultants in Toxicology, Risk Assessment and Product Safety, where she obtained and researched scientific literature for private and governmental clients. At the National Alliance for the Mentally Ill, she designed and implemented a document management and retrieval system for the Biological Psychiatry Branch of the National Institute of Mental Health and served as Managing Editor of Bipolar Network News, a newsletter for the Stanley Foundation Bipolar Network. At Howard Hughes Medical Institute, she oversaw the implementation of the Predoctoral Fellowship in Biological Sciences program. While serving as Science Information Specialist at the Distilled Spirits Council of the United States, she managed the installation of a local area network and participated in the development and maintenance of an electronic research database for the beverage alcohol industry. As a Report Coordinator at Microbiological Associates, Inc. she conducted statistical analyses and prepared technical reports about toxicology studies using animal models. She also served as Data Management Administrator for the National Toxicology Program's sponsored studies. Currently, Ms. Feldman maintains LSRO’s library, responds to requests for reports, and assists LSRO’s scientists in discovering, obtaining, compiling, and documenting the scientific literature required to prepare reports for sponsors.

Karin French, B.S. received a B.S. degree in animal science and a B.S. degree in cell and molecular biology and genetics from the University of Maryland, College Park. In addition, she earned a College Park Scholars Certificate in Science, Technology, and Society. Prior to joining LSRO as an Associate Staff Scientist, she worked in dairy nutrition at the University of Maryland, helping dairy farmers use milk urea nitrogen (MUN) to evaluate herd protein nutrition. She helped design and complete studies to compare and evaluate the MUN analysis techniques used in the National Dairy Herd Improvement Association laboratories.

Rebecca Johnson, Ph.D., received her B.A. in anthropology from Wesleyan University and her Ph.D. in anthropology, with a concentration in archaeology, from the University of Iowa. Her dissertation research examined dietary change between two Native American villages, dated to 1950 and 1600 B.P., in southeastern Iowa by looking at fatty acid residues extracted from pottery. Dr. Johnson has performed fieldwork across the Mid-Atlantic and Upper Midwest, as well as in South Carolina, Great Britain, and Poland. As the Assistant Information Specialist at LSRO, Dr. Johnson assists in maintaining the library, responding to requests for reports, and organizing the scientific literature required by staff scientists for sponsored projects. Previously, Dr. Johnson developed and maintained statewide archaeological databases for Iowa's Office of the State Archaeologist.

Catherine J. Klein, Ph.D., R.D., C.N.S.D., is a Senior Staff Scientist at LSRO. She graduated magna cum laude from the Department of Human Nutrition and Food Science at the University of Maryland, College Park, where she also obtained her M.S. and Ph.D. in nutrition. She completed internships in the Pre-Professional Practice Program in Dietetics at the University of Maryland Medical System (UMMS), Baltimore, MD, the V.A. Kleinfeld Summer Internship
Program at the Food and Drug Law Institute, Washington, D.C., Dannon’s Nutrition Leadership Institute, Wye River, MD, and most recently, the American Dietetic Association (Am Diet Assn)’s Leadership Institute, St. Petersburg, FL. At UMMS, she developed system-wide guidelines for nutrition assessment, documentation, and continuity of care. As Clinical Coordinator of Research in the Division of Critical Care Medicine at the University of Maryland R Adams Cowley Shock Trauma Center, Baltimore, MD, she developed, initiated, and administered research projects focused on nutrition issues in critical care. She established a multidisciplinary nutrition task force, which resulted in improvements in clinical practice standards. She is the primary author of 14 peer-reviewed publications, including two book chapters, and has lectured or presented at over 36 professional meetings. Dr. Klein received the Pelczar Award for Excellence in Graduate Study from the University of Maryland, Graduate School and Sigma Xi, and the Dr. E.V. McCollum Award from the Maryland Dietetic Association. Her professional contributions include serving on the Advisory Board of the University of Maryland Dietetics Program, serving as editor for the Maryland Dietetic Association, and serving a three-year term on the American Dietetic Association Quality Management Committee.
LSRO Report: Approach to Establish Guidelines for Cholesterol Intake

A.3 LIFE SCIENCES RESEARCH OFFICE BOARD OF DIRECTORS (2006)

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B.1 OVERVIEW

The National Cholesterol Education Program (NCEP) of the National Heart, Lung, and Blood Institute takes both a population-based and a clinical approach to the prevention of coronary heart disease (CHD). It identified blood low density lipoprotein (LDL)-cholesterol concentration as a primary target for both these approaches, but the clinical approach intensifies preventative strategies for higher-risk persons (National Heart Lung and Blood Institute, 2002).

In its latest report (National Heart Lung and Blood Institute, 2002), the NCEP Adult Treatment Panel III (the NCEP panel) addressed the diagnosis and management of hypercholesterolemia. It conducted a systematic literature review and selected publications for inclusion that provided relevant information. The NCEP panel categorized the strength of the evidence derived from these studies, constructed summaries in the form of evidence statements, evaluated the clinical significance of each summary statement, and developed recommendations by consensus (Grundy et al., 2004). This effort was extended by the review of an additional five clinical trials of statin therapy (Tippett & Cleveland, 1999).

Based on data from the 1994 to 1996 Continuing Survey of Food Intakes by Individuals (CSFII) as reported by Tippett & Cleveland (1988), the NCEP panel considered that average U.S. daily intake of cholesterol was 331 mg/d for men and 213 mg/d for women, with an average overall intake of 256 mg/d. During this time period, cholesterol intake was less than 300 mg/d for 79% of women and for 55% of men.

B.1.1 Evidence statements

The five major NCEP evidence statements (National Heart Lung and Blood Institute, 2002) relevant to cholesterol intake and CHD are:

1. **Multiple lines of evidence from experimental animals, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled clinical trials indicate a strong causal relationship between elevated LDL-cholesterol and CHD.** The NCEP panel categorized the strength of evidence as very strong for major randomized controlled clinical trials (RCT), smaller RCT, meta-analyses of other clinical trials, observational studies, and metabolic studies.

2. **Higher intakes of dietary cholesterol raise blood LDL-cholesterol levels in humans.** “Through this mechanism, higher intakes of dietary cholesterol should raise the risk for CHD” (National Heart Lung and Blood Institute, 2002). The NCEP panel categorized the strength of evidence as major RCT with moderately strong evidence and smaller RCT and meta-analyses with very strong evidence.

3. **An atherogenic diet is a major, modifiable risk factor for CHD.** The NCEP panel categorized the strength of evidence as very strong observational and metabolic studies. The NCEP panel concluded that high intakes of saturated fatty acids and cholesterol directly raise LDL-cholesterol concentrations. Moreover, it suggested
that certain dietary patterns appear to modify baseline risk for CHD, independent of
effects on LDL-cholesterol.

4. **Reducing cholesterol intakes from high to low decreases blood LDL-cholesterol in most persons.** The NCEP panel categorized the strength of evidence as major RCT with moderately strong evidence and smaller RCT and meta-analyses with very strong evidence.

5. **In short term, controlled clinical trials a 1% reduction in LDL-cholesterol levels, on average, reduces risk for hard CHD events (i.e., myocardial infarction and CHD death) by approximately 1%**. The NCEP panel categorized the strength of evidence as major RCT.

### B.2 EVIDENCE OF RAISED BLOOD CHOLESTEROL AND CORONARY HEART DISEASE

#### B2.1 Supplemental dietary cholesterol raises blood total cholesterol

Referring to summaries by Grundy *et al.* (1989a) and the National Research Council (2001), the NCEP panel regarded tightly controlled studies that increased cholesterol density by 100 mg/1000 calories as capable of increasing blood total cholesterol by 10 mg/dL. However, the NCEP panel qualified this estimate by acknowledging that the magnitude of blood lipid response to diet varies greatly from person to person. The NCEP panel also referred to the meta-analysis by Weggemans *et al.* (1988) which determined that dietary cholesterol was associated with unfavorably raising the ratio of blood total-to-high density lipoprotein (HDL)-cholesterol.

The paper by Grundy *et al.* (1988) summarized the 1986 workshop, “The Impact of Dietary Cholesterol on Plasma Lipoproteins and Atherogenesis,” which was co-sponsored by the National Heart, Lung, and Blood Institute and the Agricultural Research Service, U.S. Department of Agriculture. The workshop examined differing views on whether dietary cholesterol contributed to blood cholesterol and CHD. Dr. Fred Mattson, a participant in this workshop, noted that, “although not all investigations have provided identical results, when all data are averaged, the rise in plasma total cholesterol is about 10 mg/dL for every 100 mg of dietary cholesterol per 1000 calories.” The specific studies from which this generalization was derived were not identified. Grundy *et al.* (1965a) noted that according to data from Keys *et al.* (1988), the effects of reducing cholesterol intake from a baseline range of 500 mg/d to 300 mg/d may be more modest than suggested by Dr. Mattson, perhaps only 5 to 6 mg/dL per 200 mg/d reduction in intake. Most workshop participants agreed that incremental increases exceeding 500 mg/d would have little effect on blood total cholesterol. The question of whether or not incremental increases in cholesterol intakes between zero and 500 mg/d resulted in a linear or curvilinear response by blood total cholesterol remained unanswered. The range of supplemental cholesterol from 200 mg/d to 500 mg/d was of particular interest to workshop participants, yet data were lacking to resolve whether or not this level of diet modification would induce a significant rise in blood cholesterol. Grundy *et al.* (1988) estimated that for a diet of 2000 to 2500 kcal/d, reducing dietary cholesterol from 500 mg/d to 300 mg/d (e.g., by 80-100 mg/1000 kcal) would cause a reduction in blood total cholesterol of approximately 5 to 10 mg/dL. Grundy *et al.* (1992) regarded such a reduction in blood total cholesterol as leading to a reduction in coronary risk of 5% to 10%, if every 1 mg/dL drop in concentration decreased risk by approximately 1%. They suggested that such a decline would be clinically relevant for the population at-large.
B.2.2 Supplemental dietary cholesterol raises blood LDL-cholesterol

The NCEP panel considers that saturated fat and cholesterol are the major dietary constituents contributing to elevations in blood LDL-cholesterol. Based on its review of controlled metabolic studies in humans (specific studies not cited), the NCEP panel concluded that “high” cholesterol intakes raise LDL-cholesterol. The NCEP panel cited a review by Hopkins (1997) and a meta-analysis by Clarke et al. (1992) as confirming this relationship.

Hopkins (1992) identified six, relatively small studies published from 1982 to 1990 that examined the response of lipoprotein fractions to dietary changes. In three studies, normocholesterolemic individuals had no significant change in blood total cholesterol (Clifton et al., 1990; Kestin et al., 1989) or in LDL-cholesterol (Beynen & Katan, 1985) after dietary cholesterol increased by 517 mg/d, 680 mg/d, or 1500 mg/d for four weeks. Similarly, there were no significant changes in blood total cholesterol or LDL-cholesterol for six normocholesterolemic volunteers fed 6 egg yolks (reported as 1800 mg/d) for 10 days (Beynen & Katan, 1985). But when the experiment was repeated one-year later, a significant increase in blood total and LDL-cholesterol was reported compared to the mean baseline values (averaging baseline of years one and two) (1992). In the fifth study cited by Hopkins (1992), Zanni et al. (1982) reported that mean±SD blood total and LDL-cholesterol rose significantly (P < 0.05) from 136.2±25.3 and 72.4±27.2 mg/dL to 158.5±24.6 and 88.6±26.1 mg/dL, respectively, for normocholesterolemic women (n=9) after 745 mg/d cholesterol was added to a corn oil based diet for 15 days. In the sixth study cited, Schonfeld et al. (1982) reported that the ratio of polyunsaturated fat to saturated fat (P/S) in diets fed for 4-6 weeks duration influenced the blood response to dietary cholesterol. Blood total and LDL-cholesterol increased significantly in healthy young men (n=6 to 11 per experiment) after the addition of three eggs or six eggs to diets with a low (0.25-0.40) P/S ratio and after six eggs were added to diets with a moderate (0.8) P/S ratio, but not when three eggs were added to a moderate P/S diet or up to six eggs were added to a high (2.5) P/S diet (Schonfeld et al., 1982). Schonfeld et al. (Schonfeld et al., 1982) reported that “the major diet cholesterol-induced changes in total cholesterol were due to LDL-cholesterol.” The increase in LDL-cholesterol concentration was due to an increase in the number of LDL particles, not because of changes in the size, shape, density, or composition of LDL-cholesterol. Evidence from Schonfeld’s paper likely suggested to Hopkins (1992) that “changes in LDL-cholesterol accounted for most of the changes in total cholesterol.” Hopkins estimated that changes in LDL-cholesterol account for 80% to 90% of the increase in blood total cholesterol. This statement is supported by Schonfeld et al. (Schonfeld et al., 1982), but only for diets with a P/S of 0.25-0.40.

Of the 72 reports included by Clarke et al. (1997) for meta-analysis, a subset of 227 solid food experiments reported LDL-cholesterol; total number of subjects not reported. For some studies, Clarke et al. (1997) estimated mean cholesterol intake from median or mid-range values. Multivariate regression coefficients (SE) of effects per each mg/d of cholesterol in the diet were 0.0007 (0.0001) for blood total cholesterol and 0.0005 (0.0001) for LDL-cholesterol (71% of total blood cholesterol response). Further multivariate analyses by Clarke et al. (1997) indicated that isocaloric changes to replace 10% of dietary saturated fat by polyunsaturated fat (5%) and monounsaturated fat (5%) and to decrease cholesterol intake by 200 mg (e.g., 340 mg/d to 140 mg/d) was estimated to reduce blood total cholesterol by 0.76 mmol/L (SE 0.03) [29.4 (1.2) mg/dL], 99% confidence interval of 0.67 to 0.85, including a reduction in LDL-cholesterol of 0.62 (0.04) mmol/L [24 (1.6) mg/dL], 82% of total blood cholesterol response. Clarke et al. (1997) suggested that “in the average British diet, replacement of 60% of the saturated fat by
other dietary fats and avoidance of 60% of dietary cholesterol would reduce blood cholesterol by about 0.8 mmol/L (that is, by 10-15%), with four fifths of this reduction being in low density lipoprotein cholesterol,” (i.e., attributing 80% of the blood cholesterol decline to LDL-cholesterol).

B.2.3 Dietary cholesterol increases risk of coronary heart disease

Limited data was presented by the NCEP panel regarding the relationship between high intake of dietary cholesterol and development of CHD. In its discussion of saturated fat, the NCEP panel stated that epidemiological studies, specifically the Seven Countries Study (1988), show that populations consuming high amounts of saturated fat and cholesterol have a high risk for CHD.

The NCEP panel also considered a re-analysis by Stamlr & Shekelle (Shekelle et al., 1981) of epidemiological data from the Western Electric Study in Chicago (1985; McGee et al., 1984), the Honolulu Heart Program Study (Kushi et al., 1985), the Ireland-Boston Diet-Heart Study (Kromhout & de Lezenne, 1984), and ten-year follow up of the Zutphen study (Stamler & Shekelle, 1988). For these four studies, the weighted mean difference in baseline cholesterol intake between cases that developed CHD and those that did not (16 mg/1000 kcal) was significant (1988). This analysis indicated that, on average, a 200 mg/1000 kcal higher intake of cholesterol at baseline was associated with a 30% greater risk of CHD. Stamler & Shekelle (1988) considered that the observed association between baseline intake of dietary cholesterol and risk for CHD was greater than could be explained only by effects on blood total cholesterol. Hence Stamler & Shekelle (1988) suggested that dietary cholesterol may increase risk of CHD through mechanisms that are supplemental to its effects on blood total cholesterol, such as alterations in circulating lipid and lipoprotein fractions, e.g., LDL-cholesterol, or adverse effects related to thrombogenesis or for other reasons. Based on this suggestion by Stamler & Shekelle (National Heart Lung and Blood Institute, 2002), the NCEP panel considered that dietary cholesterol may increase the risk of heart disease, independent of its effect on blood LDL-cholesterol (National Heart Lung and Blood Institute, 2002). However, the NCEP panel’s primary conclusion in this matter was that higher intakes of dietary cholesterol raise blood LDL-cholesterol and it is through this mechanism that dietary cholesterol is expected to raise the risk for CHD.

B.3 EVIDENCE OF DIETARY MODIFICATION AND REDUCED CORONARY HEART DISEASE

B.3.1 Dietary modification can reduce low-density lipoprotein cholesterol

Citing the work of Howell et al.(1997), the NCEP panel qualified the expectation that reducing dietary cholesterol would reduce blood cholesterol, in that the effects achieved in the outpatient setting would probably be less than effects reported for tightly controlled metabolic studies. Adapting estimates from Jenkins et al. (National Heart Lung and Blood Institute, 2002), which were based on unpublished data, the NCEP panel predicted that a combination of several dietary modifications (e.g., restricting energy, saturated fat, and cholesterol; adding viscous fiber and plant sterols/stanols) would lead to an approximate overall reduction in LDL-cholesterol of at least 20-30 % in hyperlipidemic individuals (Hjermann et al., 1981; Miettinen et al., 1972; Turpeinen et al., 1968). Restricting dietary cholesterol to less than 200 mg/d as part of the dietary modification portfolio, was expected to decrease in blood LDL-cholesterol approximately 3–5 %.
B.3.2 Dietary modification can alter risk of coronary heart disease

The NCEP panel cited five primary prevention trials and three secondary prevention trials that tested whether lowering blood cholesterol through dietary modification, which included reduction in dietary cholesterol, would reduce the risk for CHD. These studies are described in Table B-1. An ability to reduce the incidence of myocardial infarction and/or mortality was reported for some primary prevention trials (1976; Cutler et al., 1985; Dayton et al., 1965; Dayton et al., 1969; Frantz, Jr. et al., 1989; Gorder et al., 1986), whereas other trials showed no significant difference in cardiovascular events or mortality (Ball et al., 1965; Singh et al., 1992). The results were mixed as well for the secondary prevention trials, with two studies reporting no significant difference in clinical outcome (Leren, 1966) and one study reporting a significant decline in the number of total and fatal reinfarctions (Gordon, 2000).

The NCEP panel cited a meta-analysis of clinical trials by Gordon (2000) and more recent work undertaken by Gordon and Proschan (1995; 2000) as supporting the hypothesis that diet modification can achieve as much CHD risk reduction from lower blood total cholesterol as certain drug treatments. In his initial meta-analysis, Gordon (2002) included six randomized clinical trials utilizing diet as the sole experimental treatment to lower blood cholesterol (Table B-2). These studies were conducted from mid-1960 to 1992 with follow up ranging from three to seven years. The percent blood total cholesterol reduction ranged from 4.6% to 14.4% (Table B-3). Overall, pooled results indicated that dietary intervention resulted in an 11% mean reduction in blood total cholesterol, comparable to several other types of interventions (Gordon, 1995). Later re-analysis by Gordon and Proschan, published in the NCEP report (Gordon, 2000), combined trials of dietary intervention with trials of nicotinic acid treatment with and without other medications. This combination intervention class had a 10% reduction in blood total cholesterol, similar to the 11% reduction calculated for the pooled results in the earlier analysis (Gordon, 1995; Woodhill et al., 1978).

Individually, none of the study diets resulted in significant differences in incidence of CHD or mortality (Table B-3). However, excluding the Sydney diet trial (Gordon, 2000), which did not report cause-specific mortality or nonfatal myocardial infarction by group values, pooled results suggest dietary intervention significantly decreased (-23.8%, \( P < 0.05 \)) the risk of negative outcome (incidence of nonfatal myocardial infarction or incidence of CHD mortality) (Gordon, 1995; National Heart Lung and Blood Institute, 2002).

B.4 PANEL RECOMMENDATIONS

The NCEP panel recognized that although the optimal diet for long-term prevention of CHD is still an issue under investigation, dietary modifications currently advocated are feasible. The NCEP panel reported that randomized trials (specific studies not cited) provide consistent evidence demonstrating that an interdisciplinary approach for the management of high blood cholesterol, which includes registered dietitians, results in improved patient compliance with diet therapy and other therapeutic interventions (National Heart Lung and Blood Institute, 2002).

The NCEP panel recommended lifestyle changes such as Therapeutic Lifestyle Changes (TLC), as the first-line of therapy for primary prevention of CHD. The TLC diet has replaced the Step II

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11 Published in the NCEP report, page II-43
diet, which had similar diet prescriptions. Table B-4 provides a general overview of the NCEP panel’s dietary guidance, LDL-cholesterol goals, and suggested schedule for re-evaluation based on assessment of patient risk (Grundy et al., 2004).

Any person at high-risk or moderately high risk who has life-style related risk factors (e.g., obesity, physical inactivity, elevated blood triglyceride, low HDL-cholesterol, or metabolic syndrome) is considered a candidate for TLC to modify the risk factors regardless of blood LDL-cholesterol level (National Heart Lung and Blood Institute, 2002). A reduction in intake of saturated fat and cholesterol is the core message of the TLC diet (National Heart Lung and Blood Institute, 2002). The NCEP panel was unaware of any adverse effects from the “short-term” use of such diet modification (National Heart Lung and Blood Institute, 2002).

The TLC strategies related to diet consist of:

- Reducing intake of saturated fat to less than 7% of total calories and reducing dietary cholesterol to less than 200 mg/d to lower blood LDL-cholesterol
- Other dietary modifications that might lower blood LDL-cholesterol and impact heart health, such as increasing intake of plant stanols/plant sterols to 2 g/d, consuming 10 to 25 mg/d of viscous fiber, and decreasing intake of *trans* fatty acids
- Optimizing body weight
- Enhancing physical activity

The NCEP panel did not report specific evidence or discuss the specific rationale for the selection of the 200 mg/d cut-off for cholesterol intake. The NCEP panel suggested that TLC should be intensified by “more vigorous” reduction in cholesterol intake and other modifications if the LDL-cholesterol goal is not achieved by six weeks in high risk patients (National Heart Lung and Blood Institute, 2002). NCEP treatment goals for at-risk patients were endorsed by the American Heart Association, the American College of Cardiology Foundation, and the National Heart, Lung, and Blood Institute.

The key NCEP recommendations related to dietary cholesterol are (Stone et al., 2005) (1981):

- The primary target of cholesterol lowering therapy is to lower blood LDL-cholesterol
- As part of TLC, modify atherogenic diets to reduce CHD risk
- Specifically, consume less than 200 mg/d of cholesterol, consume less than 7% of energy as saturated fat, consume 10-24 g/d of viscous fiber, and consume 2 g/d of plant stanols/sterols
### Table B-1. Studies cited by the National Cholesterol Education Program as supporting a positive trend between dietary modification and reduction of CHD.

<table>
<thead>
<tr>
<th>Description</th>
<th>Groups</th>
<th>Dietary cholesterol</th>
<th>Parameter</th>
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<tr>
<td><strong>Primary prevention trials</strong></td>
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| Hjermann *et al.* (1981) | Oslo study group. Randomized 5-year trial of low-fat diet and smoking cessation. (Individuals on low-fat diets prior to enrollment were excluded.) 1,232 normotensive men, aged 40-49 years, at high risk for CHD because of smoking habits and/or blood cholesterol. | Intervention diet (n=604); 79% smokers; baseline blood total cholesterol 290-379 mg/dL  
Control diet (n=628); 80% smokers; blood total cholesterol 290-379 mg/dL | After four years:  
Intervention subgroup (n=23) 289 mg/d cholesterol (129 mg/1000 kcal); 8% kcal as saturated fat.  
Control subgroup (n=23) 527 mg/d cholesterol (226 mg/1000 kcal); 18% kcal as saturated fat. | After four years, blood total cholesterol significantly lower for intervention group compared to control group.  
The incidence of myocardial infarction and sudden death 47% lower in intervention group than controls ($P < 0.03$). |
| Dayton *et al.* (1965; 1969) | Los Angeles Veterans Domiciliary Study. Randomized, double-blind, controlled institutional 8-year trial; Elderly men, many with physical and emotional disabilities; *ad libitum* intake of controlled diets (mean duration 32 months) | Intervention diet (n=424)  
Control diet (n=422) | Intervention diet: 365 mg/d cholesterol (146 mg/1000 kcal); 39% kcal total fat; 23% kcal saturated fat.  
Control diet provided  
>650 mg/d cholesterol (>260 mg/1000 kcal);  
≥40% kcal total fat;  
46% kcal saturated fat (Individual intakes not measured) | The intervention group had a reduction in blood total cholesterol.  
No significant differences in the primary endpoints of new myocardial infarction or sudden death. |

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<table>
<thead>
<tr>
<th>Primary prevention trials</th>
<th>Description</th>
<th>Groups</th>
<th>Dietary cholesterol</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frantz et al. (1989)</td>
<td>Minnesota Coronary Survey. Randomized, double-blind; 4393 men and 4664 women, institutionalized in state mental hospitals or a nursing home, mean duration in study was 384 days</td>
<td>Intervention diet (n=4541)</td>
<td>Intervention diet (mean) 166 mg/d cholesterol; 9% of energy as saturated fat. Control diet (n=4516)</td>
<td>No significant difference in cardiovascular events or mortality between intervention and control groups (period of follow-up not reported). Blood total cholesterol averaged 175 mg/dL in the intervention group, 203 mg/dL in the control group, in comparison to a combined baseline mean of 207 mg/dL.</td>
</tr>
<tr>
<td>Miettinen et al. (1972)</td>
<td>Long-term cross-over trial in two mental hospitals in Finland; Patients over 15 years of age were included; total of 581 men were included the first 6 years; The average diet period lasted 4 years (range: one month to six years, depending on the length-of-stay of the patient).</td>
<td>Total number of patients in groups not available</td>
<td>Intervention diet consisted of replacing whole milk, butter, and stick margarine with skim milk-added soybean oil and tub margarine; In the first 6 years (mean) 228 mg/d cholesterol (81 mg/1000 kcal); 30-32% of kcal from fat. Control diet was the regular house diet; In the first 6 years (mean) 514 mg/d cholesterol (178 mg/1000 kcal); 34-37% of kcal from fat.</td>
<td>In-hospital mortality during each 6-year study period was measured. Age-adjusted death rates from CHD per 1000 person-years were significantly lower for pooled intervention periods in men. Total blood cholesterol averaged 12 to 18% less for the intervention diet period and the incidence of electrocardiographic patterns indicative of CHD was reported to be significantly lower during the intervention period.</td>
</tr>
</tbody>
</table>
Table B-1. Studies cited by the National Cholesterol Education Program as supporting a positive trend between dietary modification and reduction of CHD.\(^a\)

<table>
<thead>
<tr>
<th>Description</th>
<th>Groups</th>
<th>Dietary cholesterol</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Heart, Lung, and Blood Institute (1976; Cutler et al., 1985; Gorder et al., 1986)</td>
<td>The Multiple Risk Factor Intervention Trial (MRFIT). Randomized, prevention trial at 22 U.S. clinical centers from 1973 to 1982. Intervention to lower blood cholesterol and diastolic blood pressure and included smoking cessation. Men 35-57 y of age (n = 12,866) with one or more CHD risk factors. Followed for 6-8 years.</td>
<td>Intervention (n=6428)</td>
<td>Intervention diet: saturated fat intake to 10% of total calories; dietary cholesterol decreased to 267 mg/d (140 mg/1000 kcal) and saturated fat decreased by &gt;25%. Usual Care diet: saturated fat intake up to 14% of total calories; cholesterol 425 mg/d (189 mg/1000 kcal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usual care (n=6438)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary prevention trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ball et al. (1965)</td>
<td>Randomized, controlled trial in 252 men recovering from myocardial infarction in Northwest London; follow up to first relapse or 5 years</td>
<td>Intervention (n=123)</td>
<td>Intervention of a maximum of 43-45 g of fat daily, eggs limited to one per day; mean fat intake 45 g in intervention group and 106-125 g in control group Dietary cholesterol not measured</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (n=129)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued next page)
### Table B-1. Studies cited by the National Cholesterol Education Program as supporting a positive trend between dietary modification and reduction of CHD.

<table>
<thead>
<tr>
<th>Description</th>
<th>Groups</th>
<th>Dietary cholesterol</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary prevention trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh et al. (1992)</td>
<td>Indian trial. Randomized, single-blinded intervention 6-week trial commencing within 48 hours after acute myocardial infarction</td>
<td>Intervention (n=204; 88% men) Control (n=202; 92% men)</td>
<td>Intervention diet: included reduced dietary cholesterol and saturated fats; 128 mg/d cholesterol (89 mg/1000 kcal); 5.5% kcal as saturated fat. Control diet: 267 mg/d cholesterol (156 mg/1000 kcal); 10.2% kcal as saturated fat.</td>
</tr>
</tbody>
</table>

| Leren et al. (1966) | Oslo trial. Randomized 412 male survivors of myocardial infarction; five year follow up | Intervention (n=206) Control (n=206) | Intervention diet: included reduction of saturated fats and cholesterol; subgroup (n=17) 264 mg/d cholesterol (111 mg/1000 kcal); 8.5% kcal as saturated fat. Control diet was the conventional diet. | After five years, significantly less number of patients in the intervention group had reinfarction; the number of fatal infarctions was significantly less as well in the intervention group. The total CHD mortality between groups was not statistically significant. |

---

*CHD: coronary heart disease; LDL: low density lipoprotein*
Table B-2. Cholesterol-lowering trials analyzed by Gordon. *

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dietary fat</th>
<th>Dietary Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Los Angeles Veterans Domiciliary (Dayton et al., 1969)</td>
<td>39%±SD2% kcal (n=424)</td>
<td>365 mg/d (146 mg/1000 kcal) (Goal: &lt; 7 egg yolks/week)</td>
</tr>
<tr>
<td></td>
<td>40%±SD2% kcal (n=422)</td>
<td>653 mg/d (262 mg/1000 kcal)</td>
</tr>
<tr>
<td>MRC low fat (1965)</td>
<td>Diet instruction for 40 g/d fat, 1 egg/d; Mean fat range: 43-45 g/d (n=123)</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>Usual diet Mean fat range: 106-128 g/d (n=129)</td>
<td>na</td>
</tr>
<tr>
<td>MRC Soya (1968; Research Committee to the Medical Research Council, 1968)</td>
<td>43 g daily of soybean or corn oil; No egg yolks, whole milk, high-fat meats, or butter; 46% kcal as fat (n=199)</td>
<td>258 mg/d (108/1000 kcal)</td>
</tr>
<tr>
<td></td>
<td>Usual diet (n=194)</td>
<td>588 mg/d (259/1000 kcal)</td>
</tr>
<tr>
<td>Oslo (Leren, 1966)</td>
<td>39% kcal as fat (n=206)</td>
<td>(n=17) 216 mg/d (111 mg/1000 kcal)</td>
</tr>
<tr>
<td></td>
<td>(n=206)</td>
<td>na</td>
</tr>
<tr>
<td>STARS (Watts et al., 1992)</td>
<td>Diet instruction for 27% kcal as fat (n=27)</td>
<td>Diet instruction for 100 mg/1000 kcal</td>
</tr>
<tr>
<td></td>
<td>Usual care (n=28)</td>
<td>Usual care</td>
</tr>
<tr>
<td>Sydney Diet-Heart Study (Woodhill et al., 1978)</td>
<td>Diet instruction for 10% kcal as saturated fat (n=221)</td>
<td>Mean±SD: 248±75 mg/d (108 mg/1000 kcal)</td>
</tr>
<tr>
<td></td>
<td>Usual diet (n=237)</td>
<td>Mean±SD: 342±103 mg/d (156 mg/1000 kcal)</td>
</tr>
</tbody>
</table>

*LDL: low density lipoprotein; MRC: Research Committee to the Medical Research Council; na: data not available; STARS: St. Thomas Atherosclerosis Regression Study.
Table B-3. Incidence of coronary heart disease and mortality in randomized trials of cholesterol lowering diets (6356 person-yr)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Trial</th>
<th># Persons</th>
<th>FU (yr)</th>
<th>Percent cholesterol reduction</th>
<th>Total</th>
<th>CHD</th>
<th>Non-CHD</th>
<th>CHD incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trt</td>
<td>Ctrl</td>
<td></td>
<td>Trt</td>
<td>Ctrl</td>
<td>OR</td>
<td>Trt</td>
</tr>
<tr>
<td>Los Angeles Veterans Domiciliary (1969)\textsuperscript{b}</td>
<td>424</td>
<td>422</td>
<td>7.0</td>
<td>12.7</td>
<td>174</td>
<td>177</td>
<td>0.96</td>
</tr>
<tr>
<td>MRC low fat (1965)</td>
<td>123</td>
<td>129</td>
<td>3.0</td>
<td>9.3</td>
<td>20</td>
<td>24</td>
<td>0.85</td>
</tr>
<tr>
<td>MRC Soya (1968)</td>
<td>199</td>
<td>194</td>
<td>4.0</td>
<td>14.2</td>
<td>28</td>
<td>31</td>
<td>0.86</td>
</tr>
<tr>
<td>Oslo (1966)</td>
<td>206</td>
<td>206</td>
<td>5.0</td>
<td>14.4</td>
<td>41</td>
<td>55</td>
<td>0.68</td>
</tr>
<tr>
<td>STARS (1992)</td>
<td>27</td>
<td>28</td>
<td>3.3</td>
<td>11.0</td>
<td>1</td>
<td>3</td>
<td>0.36</td>
</tr>
<tr>
<td>Sydney (1978)</td>
<td>221</td>
<td>237</td>
<td>5.0</td>
<td>4.6</td>
<td>39</td>
<td>28</td>
<td>1.59</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Meeting the following criteria: (1) analyzed by intent to treat, (2) not confounded, (3) at least 3 years duration, (4) at least 4% cholesterol reduction. CHD = coronary heart disease; Ctrl = Control group; FU = follow up; MRC = Research Committee to the Medical Research Council; OR = odds ratio; (Trt. \textit{versus} Ctrl.), STARS: St. Thomas’ Atherosclerosis Regression Study; Trt. = Active treatment group. \textsuperscript{b} Primary prevention trial.

None of the results from the individual trials were statistically significant for Trt \textit{versus} Ctrl. From Gordon (National Heart, Lung, and Blood Institute, 2002).
Table B-4. National Cholesterol Education Program therapeutic approaches for diet guidance and therapy (Grundy et al., 2004)*

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Measured LDL-cholesterol (mg/dL)</th>
<th>Diet Guidance</th>
<th>Goal LDL-cholesterol (mg/dL)</th>
<th>Suggested Schedule for Re-evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1 Risk factors</td>
<td>&lt; 130</td>
<td>U.S. dietary guidelines &lt; 300 mg/d</td>
<td>&lt; 160 mg/dL</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td>130 – 159</td>
<td>U.S. dietary guidelines &lt; 300 mg/d</td>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td>≥ 160</td>
<td>TLC &lt; 200 mg/d</td>
<td></td>
<td>3 months</td>
</tr>
</tbody>
</table>

| 2+ Risk factors 10-y risk < 20% by Framingham scoring | < 130 | U.S. dietary guidelines < 300 mg/d | < 130 mg/dL (< 100 mg/dL is a therapeutic option for moderately high risk persons) (Grundy et al., 2004) | 1 year |
|                                                        | ≥ 130 | TLC < 200 mg/d                      |                               | 3 months                            |

| Has CHD or CHD risk equivalents                    | < 100 | TLC < 200 mg/d                      | < 100 mg/dL (or < 70 mg/dL when risk is very high) (1989a) | Monitoring and follow up in 6-weeks or sooner, as needed |
|                                                 | ≥ 100  |                                    |                                                               |                                                     |

*CHD: coronary heart disease; LDL: low density lipoprotein; TLC: Therapeutic Lifestyle Changes
C.1 OVERVIEW

The National Research Council’s publication *Diet and Health-Implications for Reducing Chronic Disease Risk* (National Research Council, 1989a) recommended limiting cholesterol intake to less than 300 mg/d. In making this recommendation, the multidisciplinary Committee on Diet and Health of the Food and Nutrition Board (the DH Committee) acknowledged the difficulty in relating the complex mixture of individual diets to development of chronic disease, in which long exposures to dietary factors are required for the manifestation of effects (National Research Council, 1989a). The DH Committee documented the strengths and limitations of epidemiologic and experimental studies of diet and chronic disease and noted the criteria for assessing this data. To arrive at their conclusions, the DH Committee gave special attention to dietary interactions and competing risks. For example, the recommendation to increase intake of low-fat dairy products integrated the advantage for bone-health provided by a rich source of calcium with efforts to minimize intake of saturated fat and cholesterol and reduce the risk of coronary heart disease (CHD). The DH Committee also took into consideration genetic variability among individuals and variability due to other factors that may alter individual response to dietary cholesterol and risk of CHD (Beveridge et al., 1960; Connor et al., 1961a; Connor et al., 1961b).

C.2 EVIDENCE THAT DIETARY CHOLESTEROL ALTERS BLOOD CHOLESTEROL AND RISK OF CORONARY HEART DISEASE

C2.1 Supplemental dietary cholesterol raises blood cholesterol

The DH Committee suggested that high intake of cholesterol may produce detrimental effects similar to that of saturated fat. Support for this hypothesis was derived from feeding studies which supplemented with as much as 3600 mg/d of cholesterol and achieved an increase in blood total cholesterol (Connor et al., 1961b). Total blood cholesterol increased sharply as cholesterol intake increased from approximately 15 mg/d to 600 mg/d (Beveridge et al., 1960). The dose-response curve was variable for increases in dietary cholesterol above 600 mg/d (National Research Council, 1989a).

After reviewing several studies of healthy subjects who consumed controlled diets supplemented with cholesterol, the DH Committee suggested that changes in blood cholesterol concentration in response to dietary cholesterol were principally due to changes in low density lipoprotein (LDL)-cholesterol (1979). In a study by Applebaum-Bowden et al. (1982), four volunteer subjects ingested a liquid-formula diet containing approximately 20 egg yolks (previously frozen) per day for 30 days. This high cholesterol diet led to marked increases in apolipoprotein B and LDL-cholesterol levels whereas other lipid fractions increased only slightly or not at all. In other studies, after healthy subjects ingested six egg yolks daily as a source of supplemental cholesterol, Schonfeld et al. (1983) and Packard et al. (1981) measured an average 25% to 40% increase in LDL-cholesterol, respectively, and Mistry et al. (1965; 1986) determined the increase of LDL-cholesterol after this level of egg consumption, on average, accounted for 58% of the increment in blood total cholesterol.
C.2.2 Estimating effects of diet on blood cholesterol

Researchers in the late 1950’s and 1960’s developed linear regression equations to predict the response of blood total cholesterol to changes in dietary fat and cholesterol intake for groups of individuals. Building upon previous work, Hegsted (1965) published a modified formula:

$$\Delta \text{Chol} = 2.16 S - 1.65 P + 0.176 C$$

where change in blood total cholesterol in mg/dL ($\Delta \text{Chol}$) is proportional to the change in intake of saturated fat (S) and polyunsaturated fat (P) in percent of calories and the change in dietary cholesterol in mg/1000 kcal (C). Note that 6.77 C in decigrams/2600 kcal in the earlier paper (Hegsted, 1986) is the same as the 0.176 C in milligrams/1000 kcal in the later paper (Hegsted et al., 1965).

In this formula, saturated fat intake accounts for 72% of the variation in blood total cholesterol concentrations, dietary cholesterol produces a small yet positive effect, and polyunsaturated fat intake has an inverse relationship with blood total cholesterol (1986). Because of the modest correlation between intakes of saturated fat and cholesterol, Hegsted (1986) was concerned that his multiple regression equation attributed too much of the blood lipid effect from dietary cholesterol and too little from saturated fat. He then generated a predictive equation specific to the relationship of dietary cholesterol and blood total cholesterol:

$$\Delta \text{Chol} = 0.0974 C$$

Change in blood total cholesterol in mg/dL ($\Delta \text{Chol}$) is proportional to the change in dietary cholesterol in mg/1000 kcal (C). Hegsted (1986) determined the association of dietary cholesterol and blood total cholesterol to be essentially linear from 0 to 400 mg/1000 kcal.

The DH Committee (National Research Council, 1989a) combined the two Hegsted equations as:

$$\Delta \text{Chol} = 2.16 S - 1.65 P + 0.0974C$$

Because dietary cholesterol elicits different responses among individuals, the DH Committee suggested that approximately 20% of individuals are likely to have a response 10% higher than predicted by these equations (National Research Council, 1989a). The DH Committee estimated that, in general, at least one-third of the population responds substantially to dietary cholesterol yet there is no practical means to identify susceptible individuals. Those that respond with an increase in blood cholesterol may not be effectively suppressing endogenous production to balance total body cholesterol (Stamler & Shekelle, 1988).

C.2.3 Dietary cholesterol is associated with risk of coronary heart disease

The DH Committee reviewed the relationship between dietary cholesterol and CHD reported by Shekelle (1981; 1982) from four long-term cohort studies: the Western Electric Study (Kromhout et al., 1985; Kromhout & de Lezenne, 1984), the Zutphen Study (1985); the Ireland-Boston Diet Heart Study (1985; McGee et al., 1984), and the Honolulu Heart Program (National Research Council, 1989a). The DH Committee noted that when cholesterol intake was assessed at entry and expressed in mg/1000 kcal, it was positively associated with risk of CHD after adjustment for age, blood pressure, cigarette smoking and blood total cholesterol level (Stamler & Shekelle,
LSRO Report: Approach to Establish Guidelines for Cholesterol Intake

1988). Using multiple logistic regression coefficients from the four studies, Stamler & Shekelle (1988) calculated that, on average, a 200 mg/1000 kcal higher intake of cholesterol at baseline was associated with a 30% greater risk of CHD. Although it recognized several confounding problems, such as the difficulty in measuring cholesterol intake, the variability in individual blood responses to cholesterol intake, and the multiple factors contributing to CHD, the DH Committee interpreted these studies as supporting an etiologic role for dietary cholesterol in CHD. Because Stamler & Shekelle (1988) found that the association of dietary cholesterol and CHD to persist after adjusting for blood total cholesterol, the DH Committee hypothesized that dietary cholesterol may exert its effect on CHD by increasing LDL-cholesterol as well as perhaps by other as-of-yet unidentified means (Gordon et al., 1982).

C.2.4 Fat-reduction diets alter blood cholesterol

The DH Committee cited a hyperlipoproteinemia treatment trial by Gordon et al. (1982), which indicated that fat-reduction diets alter LDL-cholesterol. In this study, the average cholesterol intake, obtained from 6494 hypercholesterolemic men by 24-hour recall, decreased from 407±4 mg/d (174±1 mg/1000 kcal) to 299±2 mg/d (147±1 mg/1000 kcal) after diet instruction (Gordon et al., 1982). The resulting 23.5 mg/dL decline in mean±SE blood total cholesterol was attributed to a 21.6 mg/dL decline in the LDL fraction (estimated from measures of total cholesterol, HDL-cholesterol, and triglyceride) (Gordon et al., 1982). Multiple regression modeling by Gordon et al. (Gordon et al., 1982) specified that saturated fat intake, which declined from 39±0.1 to 26±0.2 percent of total calories, was a stronger predictor of blood cholesterol concentration than dietary cholesterol. Although weak, the association of dietary cholesterol and blood cholesterol was independent of saturated fat intake.

C.3 CONCLUSIONS AND COMMITTEE RECOMMENDATIONS

The DH Committee (National Research Council, 1989a) concluded that for the population overall, the evidence from Stamler & Shekelle (Stamler & Shekelle, 1988) and others indicated that dietary cholesterol contributes to the development of CHD. The observed relationship between intake of dietary cholesterol and risk of CHD persisted after adjustment for blood total cholesterol, so the effects of dietary cholesterol were presumed to be independent of blood total cholesterol. On page 227 (National Research Council, 1989a), the DH Committee estimated that for individuals whose blood total cholesterol is in the upper range, each 1% reduction in blood total cholesterol concentration would lead to an approximately 2% reduction in CHD rates after 5 to 7 years and an even greater reduction in CHD after decades.

C.3.1 Approaches for reducing risk of coronary heart disease

The DH Committee suggested a coordinated strategy to reduce blood cholesterol and risk of CHD. The first approach was to shift the distribution of blood cholesterol levels in the entire population to a lower range by making public health recommendations for dietary modifications. The second approach was for the medical community to identify individuals at high risk of CHD and intervene on an individual basis to reduce risk factors (National Research Council, 1989a).

C.3.2 Numerical threshold for cholesterol intake

The DH Committee preferred to recommend a numerical value as a threshold for intake because such a specific target for dietary modification would be less susceptible to misinterpretation when translated into food choices (National Research Council, 1989a). The DH Committee
recommended that all adults and children over two years of age in North America limit their intake of dietary cholesterol to 300 mg/d. It offered suggestions for how to limit intake of egg yolks, shellfish, and animal fats (e.g., restrict chicken skin, whole-fat dairy) and suggested substituting fish and lean meats for higher-fat meats to curtail cholesterol intake. The specific rationale for the selection of a cut-off of 300 mg/d was not discussed in the DH Committee report. The DH Committee concluded on page 201 that, “On average, 100 mg of dietary cholesterol per 1000 kcal elevates LDL-cholesterol by 8 to 10 mg/dL.” No references were cited but this range is consistent with the equation by Hegsted (National Institutes of Health, 1985; 2006; Office of Medical Applications of Research of the National Institutes of Health, 1985). Then on page 226, when the DH Committee discussed children over two years of age, it noted several consensus recommendations including that of the National Institutes of Health (NIH) consensus conference (National Institutes of Health, 1985), which advised all Americans over the age of two years to reduce daily cholesterol intake from about 450 mg/d to 250-300 mg/d or less. No evidence was cited for this specific cut-off range. The Chair of the Consensus Development panel later wrote “The other tough issue was what dietary recommendations to make. After much discussion, we came up with guidelines very much like those adopted previously by the American Heart Association, namely, to exercise and reduce total calories to maintain normal body weight; decrease total calories from dietary fat to 30% (less than 10% from saturated fat); and reduce total daily cholesterol to less than 300 mg” (National Institutes of Health, 1985). During the NIH consensus conference, several dissenting opinions on the merits of promoting an untested diet—namely the “prudent” diet—to the general public were voiced by invited speakers and by commentators from the floor (National Heart Lung and Blood Institute, 2002). The consensus conference document has since been superceded by the National Cholesterol Education Program report (National Research Council, 1989a).

The DH Committee (National Research Council, 1989a) decided to recommend limiting cholesterol intake to “100 mg or less per 1000 kcal—not to exceed 300 mg/d.” This is similar to a 1983 recommendation from the American Heart Association, that children over two years of age should consume approximately 100 mg/1000 kcal, not to exceed 300 mg/d (Weidman et al., 1983). Thus, the DH Committee’s (American Heart Association Committee on Nutrition, 1968) cut-off of 100 mg per 1000 kcal and 300 mg/d, provides for an upper intake of 3000 kcal/d.
### APPENDIX D. SUMMARY TABLE OF KEY U.S. PUBLICATIONS AND AUTHORITATIVE RECOMMENDATIONS FOR DIETARY CHOLESTEROL FOR HEALTHY AMERICANS

<table>
<thead>
<tr>
<th>Authoritative Source</th>
<th>Publication</th>
<th>Recommendation for General Population</th>
<th>Recommendation for High-risk Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA</td>
<td><em>Diet and Heart Disease</em> <em>(American Heart Association Committee on Nutrition, 1968)</em></td>
<td>A substantial reduction of cholesterol in the diet (from level at that time of approximately 600 mg/d)</td>
<td>Reduction to &lt; 300 mg/d for hypercholesterolemic patients.</td>
</tr>
<tr>
<td></td>
<td><em>Diet in the Healthy Child</em> <em>(Weidman et al., 1983)</em></td>
<td>Daily cholesterol intake by healthy children over the age of two years should be approximately 100 mg/1000 kcal, not to exceed 300 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>AHA Dietary Guidelines: revision 2000</em> <em>(Krauss et al., 2000)</em></td>
<td>Although there is no precise basis for selecting a target level for cholesterol intake for all individuals, &lt; 300 mg/d on average is recommended.</td>
<td>Further reduction in intake is recommended for individuals with elevated LDL-cholesterol levels, diabetes, or cardiovascular disease.</td>
</tr>
<tr>
<td></td>
<td><em>Diet and Lifestyle Recommendations Revision 2006</em> <em>(Lichtenstein et al., 2006)</em></td>
<td>Recommendations include: balance caloric intake and physical activity to achieve and maintain a healthy body weight, limit intake of saturated fat to &lt; 7% of energy, limit trans fat to &lt; 1% of energy, and limit dietary cholesterol to &lt; 300 mg/d.</td>
<td>For certain patients at higher risk, AHA stated that the recommendations may have to be intensified, but gave no further instruction.</td>
</tr>
</tbody>
</table>

(Continued next page)
<table>
<thead>
<tr>
<th>Authoritative Source</th>
<th>Publication</th>
<th>Recommendation for General Population</th>
<th>Recommendation for High-risk Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA</td>
<td>Dietary Recommendations for Children and Adolescents: A Guide for Practitioners (Gidding et al., 2006)</td>
<td>No specific recommendations for dietary cholesterol. The authors state their general recommendations “echo other recent public health dietary guidelines in emphasizing low intakes of saturated and trans fat, cholesterol, and added sugar and salt,” and refer practitioners to the Dietary Guidelines for Americans (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2005) and the Pediatrician Nutrition Handbook (American Academy of Pediatrics, 2004).</td>
<td>Referred to the NCEP (National Research Council, 1989a), which “generally recommends restriction of saturated fat intake to &lt; 7% of total calories and restriction of cholesterol intake to &lt; 200 mg/d for treatment of elevated LDL-cholesterol levels.”</td>
</tr>
<tr>
<td>National Research Council; Institute of Medicine</td>
<td>Diet and Health: Implications for Reducing Chronic Disease Risk (National Research Council, 1989a)</td>
<td>Limit cholesterol intake to &lt; 300 mg/d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dietary Reference Intakes (Institute of Medicine, 2005b)</td>
<td>Cholesterol consumption should be as low as possible while consuming a nutritionally adequate diet. A Tolerable Upper Intake Level was not set.</td>
<td></td>
</tr>
<tr>
<td>Inter-Society Commission for Heart Disease Resources</td>
<td>Primary Prevention of Atherosclerotic Diseases (1970)</td>
<td>The general public should reduce dietary cholesterol to &lt; 300 mg/d (and avoid consumption of egg yolks).</td>
<td>Individuals with marked increase in risk of premature atherosclerotic diseases, should reduce dietary cholesterol to &lt; 300 mg/d (and avoid consumption of egg yolks).</td>
</tr>
<tr>
<td></td>
<td>Optimal Resources for Primary Prevention of Atherosclerotic Diseases (Kannel et al., 1984)</td>
<td>Dietary cholesterol should be reduced (from 400 mg/d intake at that time for men) to &lt; 250 mg/d (this is a further reduction from the 300 mg/d maximum advocated in 1970).</td>
<td></td>
</tr>
</tbody>
</table>

(Continued next page)
<table>
<thead>
<tr>
<th>Authoritative Source</th>
<th>Publication</th>
<th>Recommendation for General Population</th>
<th>Recommendation for High-risk Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP</td>
<td><em>The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)</em> (National Heart, Lung, and Blood Institute, 2002)</td>
<td>Any person at high or moderately high risk, having life-style related risk factors (<em>i.e.</em>, obesity, physical inactivity, elevated blood triglyceride, low HDL-cholesterol, metabolic syndrome) is considered a TLC candidate. TLC includes &lt; 200 mg/d dietary cholesterol. TLC should be intensified by “more vigorous” reduction in cholesterol intake and other modifications if LDL-cholesterol goal is not achieved by 6-weeks in high risk patients.</td>
<td></td>
</tr>
<tr>
<td>FDA</td>
<td><em>The Food Label</em> (1999)</td>
<td>Cholesterol <em>per</em> serving must be expressed on food labels as a percentage of the Daily Value; the Daily Value for cholesterol is an upper limit of 300 mg</td>
<td></td>
</tr>
</tbody>
</table>

(Continued next page)
<table>
<thead>
<tr>
<th>Authoritative Source</th>
<th>Publication</th>
<th>Recommendation for General Population</th>
<th>Recommendation for High-risk Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>USDA; DHHS</td>
<td><em>Healthy People: The Surgeon Generals’ Report on Health Promotion and Disease Prevention</em> (1979)</td>
<td>Americans would probably be healthier, as a whole, if they consumed less saturated fat and cholesterol. People should adopt prudent dietary habits, consuming less saturated fat and cholesterol.</td>
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<td></td>
<td><em>Dietary Guidelines for Americans</em> (1995)</td>
<td>Referring to the 300 mg Daily Value for cholesterol in the Nutrition Facts panel on food product labels, it was suggested that cholesterol intake be at this level or lower by eating more grain products, vegetables and fruits, and by limiting intake of high cholesterol foods. (This was the first edition of U.S. dietary guidelines to suggest a numerical goal for cholesterol intake).</td>
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<td></td>
<td><em>Dietary Guidelines for Americans</em> (2005)</td>
<td>Cholesterol intake should be kept as low as possible, within a nutritionally adequate diet, &lt; 300 mg/d of dietary is recommended for adults with an LDL-cholesterol &lt; 130 mg/dL.</td>
<td>&lt; 200 mg/d of dietary cholesterol is recommended for adults with LDL-cholesterol ≥130 mg/dL.</td>
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<td></td>
<td><em>Dietary Goals for the United States</em> (1977)</td>
<td>Goal 6, “reduce cholesterol consumption to about 300 grams (sic) a day;” this dietary goal was to be achieved, on average, over several days, and was the center of a range (250 to 350 mg) of recommended intake (see page XXVI of that report).</td>
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Dr Lisa Jackson
Scientific Advisory Committee on Nutrition
Food Standards Agency
Room 821B
Aviation House
125 Kingsway
London
WC2B 6NH

16 August 2001

Dear Dr Jackson

We would like to request that the Scientific Advisory Committee on Nutrition (SACN) consider and update past government advice in relation to dietary cholesterol, egg intake and cardiovascular disease (CVD), as part of its rolling review of scientific evidence.

As you will be aware, the 1994 COMA report recommended that the average dietary cholesterol intake (approximately 245mg/day) should not rise and that egg intake, at only 2/week, should not increase: advice that is still perceived as "current" government advice.

As I'm sure you are aware, available data does not support this advice and in particular the need for a population-wide restriction of dietary cholesterol to reduce CVD risk.

Current research suggests that dietary cholesterol has no significant effect on the LDL/HDL ratio, a recognised marker of CVD risk (Hu et al 1999, Howells et al 1997). However, encouraging a reduction in saturated fatty acid (SFA) intake is still an area that needs addressing. As eggs are relatively low in SFA (1.8g/medium egg), we believe that the advice to restrict egg intake is no longer appropriate.

In accordance with this research, it seems pertinent to highlight that even in the 1994 report, COMA acknowledged that blood cholesterol levels are more adversely affected by the amount of SFA in the diet rather than the amount of dietary cholesterol.

Following the publication of numerous studies in the last ten years, the American Heart Association has recently revised its guidelines, acknowledging that individuals can eat an egg a day if the remaining...
cholesterol in their diet is limited (by following a diet low in SFA). We believe the FSA should now issue similar advice for the UK.

We are particularly concerned that despite our publishing recent research showing that it is SFA in the diet, rather than dietary cholesterol that adversely affects CVD risk, many people are still cutting eggs out of their diet unnecessarily because of the belief that they shouldn't eat more than 2 or 3 a week. In many cases they mistakenly believe that this negates the need for them to reduce their SFA intake. Our consumer research has repeatedly shown this to be a key factor in the decline in egg consumption over the past few decades.

The health professional sector is also in need of up-to-date information. Although many individual dietitians and other health professionals would like to encourage people to eat more eggs, in line with the ‘evidence base’, because of their high nutrient content and low cost, the current ‘on the record’ advice from officials does not support this.

We feel it timely that UK advice should change and would therefore like to formally request that SACN review UK advice on egg intake.

I have attached some further details and papers for your information; however if you would like to discuss any of the above points in more detail, please don't hesitate to call.

Yours sincerely

Amanda Cryer

BEIS/letter/sacn 13801
Mr A Cryer  
British Egg Information Service  
126-128 Cromwell Road  
London  
SW7 4ET

20 November 2001

Dear Mr Cryer,

Thank you for your letter requesting that SACN consider and update past government advice in relation to dietary cholesterol, egg intake and cardiovascular disease.

We have considered the evidence which you cite, other recent reviews on the subject, as well as the most recently published advice of the American Heart Association. I have also discussed the issue with the Chairman of SACN, Professor Alan Jackson.

COMA advice did not prescribe a limit on egg consumption of 2/week. COMA advice suggests no rise in cholesterol consumption from an average of 245 mg/day. As one egg yolk contains about 200 mg cholesterol, this simply means that egg consumption must be taken in the context of the rest of the diet. Most sources of saturated fats, such as meat and dairy products, are also sources of cholesterol. Therefore, any advice must take into account the whole diet.

The paper you quote by Frank Hu concluded that consumption of up to one egg per day is unlikely to have substantial overall impact on the risk of CHD or stroke among healthy men and women. However, they did find an apparently increased risk of CHD associated with higher egg consumption in diabetic patients, which warranted further study.

The American Heart Association advice, which you also mention, advocates a population wide limitation of dietary cholesterol to <300mg/d, and lower intakes for individuals based on blood cholesterol and lipoprotein levels and the presence of existing diseases such as heart disease or diabetes. The AHA do not say specifically that individuals can eat an egg per day, but state that targets for cholesterol levels can readily be achieved even with ‘periodic’ consumption of eggs and shellfish.

Several studies have shown that dietary cholesterol not only increases levels of LDL cholesterol but also concentrations of HDL cholesterol. The ratio of total to HDL cholesterol involves the opposing effects of LDL and HDL cholesterol on coronary heart disease risk. As a result, the ratio is a better predictor of CHD risk than are individual lipoprotein concentrations.

Recently, Weggemanns etal, 2001, reviewed all well-controlled studies investigating the effect of dietary cholesterol from egg intake on the ratio of
total to HDL cholesterol concentrations in humans. Dietary cholesterol was shown to raise the ratio of total to HDL cholesterol and, therefore, adversely affect the cholesterol profile. Consequently, the 1994 COMA recommendation 'that average dietary intake of cholesterol should not rise' still appears valid.

Our present advice does not preclude egg consumption, nor prescribe a specific limit on egg consumption. Nutrient based advice must also, however, take into account the diet as a whole, as eggs are not the only source of cholesterol in the diet.

Yours sincerely,

Dr Lisa Jackson

cc: Professor Alan Jackson
    Dr Sheela Reddy
    Mr Tom Murray
### APPENDIX F. ACRONYMS AND GLOSSARY

#### F.1 ACRONYMS AND ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>AEB</td>
<td>The American Egg Board</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>BEIS</td>
<td>British Egg Information Service, of the British Egg Industry Council</td>
</tr>
<tr>
<td>CCCC</td>
<td>Canadian Consensus Conference on Cholesterol</td>
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<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
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<tr>
<td>COMA</td>
<td>Committee on Medical Aspects of Food Policy</td>
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<tr>
<td>CSFII</td>
<td>Continuing Survey of Food Intakes by Individuals (USDA)</td>
</tr>
<tr>
<td>DGAC</td>
<td>Dietary Guidelines Advisory Committee</td>
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<tr>
<td>DH</td>
<td>Committee on Diet and Health (Food and Nutrition Board)</td>
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<tr>
<td>DHHS</td>
<td>U.S. Department of Health and Human Services</td>
</tr>
<tr>
<td>DRI</td>
<td>Dietary Reference Intakes</td>
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<tr>
<td>EAR</td>
<td>Estimated average requirement</td>
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<tr>
<td>EHN</td>
<td>European Heart Network</td>
</tr>
<tr>
<td>ENL</td>
<td>Vegetarian food group that includes eggs, nuts, and legumes</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agricultural Organization (United Nations)</td>
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<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
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<tr>
<td>FNB</td>
<td>Food and Nutrition Board (IOM)</td>
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<tr>
<td>FSANZ</td>
<td>Food Standards Australia New Zealand</td>
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<tr>
<td>Guidelines</td>
<td>Nutrition and Your Health: Dietary Guidelines for Americans</td>
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<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
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<tr>
<td>HEI</td>
<td>Healthy Eating Index</td>
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<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
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<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LSRO</td>
<td>Life Sciences Research Office, Inc</td>
</tr>
<tr>
<td>Macronutrient Panel</td>
<td>The Panel on DRI for Macronutrients</td>
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<tr>
<td>MPFEN</td>
<td>Pyramid food group that includes meat, poultry, fish, eggs, and nuts</td>
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<tr>
<td>MRC</td>
<td>Research Committee to the Medical Research Council</td>
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<tr>
<td>MRFIT</td>
<td>Multiple Risk Factor Intervention Trial</td>
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<tr>
<td>NACNE</td>
<td>National Advisory Committee for Nutrition Education</td>
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<tr>
<td>NCEP</td>
<td>National Cholesterol Education Program</td>
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<tr>
<td>NDNS</td>
<td>National Diet and Nutrition Survey</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<tr>
<td>NHF</td>
<td>National Heart Foundation</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council (Commonwealth Department of Health and Ageing in Australia)</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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Association is observed when two events occur together more often than one would expect by chance (Strom, 2000).

Case-control studies are studies that examine differences in antecedent exposures by comparing cases with a disease to control subjects without the disease (Strom, 2000).

Case series are reports of patients grouped by exposure/treatment or by outcome. In those studies that group patients by exposure/treatment, the patients various clinical outcomes would be described. For those studies grouping patients by disease/outcome, the variables that might be common among them would be investigated to raise hypotheses about what might have contributed to the development of the disease of interest (National Heart, Lung, and Blood Institute, 2002).

Cohort studies follow defined populations forward in time to determine their rates of disease. In these studies, individuals exposed to the factor of interest are compared to those who are not exposed or who are exposed to a different factor (Strom, 2000).

Coronary heart disease (CHD) risk equivalents are conditions that carry an absolute risk for developing new CHD equal to the risk of having recurrent CHD events (i.e., myocardial infarction and coronary death) in persons with established CHD. Such conditions include symptomatic carotid artery disease, peripheral artery disease, type 2 diabetes mellitus, abdominal aortic aneurysm or 10-year risk for CHD greater than 20% (see Framingham point scoring) (National Heart Lung and Blood Institute, 2002).
Cross-sectional studies measure variables in subjects at one point in time.

Descriptive studies do not include a control group. Case reports, case series, and analyses of secular trends are types of descriptive studies (National Heart, Lung, and Blood Institute, 2002).

Framingham point scoring is used to assign 10-year risk of CHD in one of three categories: less than 10% risk, 10 to 20% risk, or greater than 20% risk (a CHD risk equivalent). The risk factors included in calculating scores are: age, total cholesterol, HDL-cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking (National Heart, Lung, and Blood Institute, 2002).

INTERLIPID Study is an ancillary study to the INTERMAP study and focuses on comparisons between participants in Japan and Japanese-American participants in Hawaii.

INTERMAP Study is a multinational epidemiological investigation of the role of multiple dietary factors and other lifestyle factors that account for individual differences in blood pressure. Sample and data collection includes four 24-hour dietary recalls, two 24-hour urine samples, and blood samples from 4680 participants in four age/gender strata in China, Japan, the United States, and the United Kingdom.

Lowest-observed-adverse-effect level is the lowest intake or experimental oral dose at which an adverse effect has been observed in the individuals studied.

Meta-analysis is a systematic statistical method to aggregate and re-analyze previously published findings from different sources of a particular treatment or exposure to provide an overall measure of effect.

Multiple (+2) risk factors for coronary heart disease (CHD). For the clinical purpose of setting category of risk, the following subset of CHD risk factors are counted: older age, low blood concentration of high density lipoprotein cholesterol, hypertension or treatment for hypertension, family history of premature CHD, and cigarette smoking. Based on this score, the risk factor category is expressed as either 0 – 1 risk factor or multiple (+2) risk factors. An individual with established CHD or CHD risk equivalents is in a third risk category, which is higher than an individual having multiple (+2) risk factors without CHD or CHD equivalents (see Risk factors for CHD).

No-observed-adverse-effect level is the highest intake or experimental oral dose at which no adverse effects are observed in the individuals studied.

Primary prevention in this report denotes the prevention of coronary heart disease (see Secondary prevention).

Risk factors for coronary heart disease (CHD) Increasing age, male sex, and a strong family history of heart disease are not modifiable risk factors for CHD. The modifiable risk factors include cigarette smoking, high blood pressure, high blood cholesterol, physical inactivity, an atherogenic diet, obesity, and diabetes. An individuals response to stress and excessive alcohol consumption may also be contributing factors (see Multiple (+2) risk factors) (National Heart, Lung, and Blood Institute, 2002).
Secondary prevention in this report denotes the prevention of recurrent coronary heart disease (see Primary prevention).

10-year risk of coronary heart disease (see Framingham point scoring)

Tolerable upper Intake Level (UL) is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increase above the UL, the risk of adverse effects increases. The UL is not a recommended level of intake (Institute of Medicine, 2005b).

Vegan characterizes an individual as one who abstains from eating all animal products (e.g., meat, fish, milk, eggs) and characterizes a diet or food as being free from any animal product.

Viscous fiber (e.g., soluble fiber). A nondigestible carbohydrate or lignin component of plants that, when ingested, can delay gastric emptying creating a sensation of fullness and reducing peak postprandial blood glucose concentration. Viscous fibers also can interfere with absorption of dietary fat and cholesterol (Institute of Medicine, 2005b).