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

## EXECUTIVE SUMMARY

November 2006

Catherine J. Klein, Ph.D., R.D.

Prepared for The American Egg Board, 1460 Renaissance Drive, Park Ridge, Illinois 60068.

**This is a brief summary of the review by LSRO. It is not a complete document and should be considered within the context of the full report, which can be obtained at WWW.LSRO.ORG**



---



Copies of this publication may be obtained from Life Sciences Research Office. Orders and inquiries may be directed to LSRO, 9650 Rockville Pike, Bethesda, MD 20814.
Phone: 301-634-7030. Fax: 301-634-7876. Website: www.LSRO.org.

ISBN: 0-9753167-6-1
Library of Congress Catalog Number: 2006937647

# 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."[1] 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.

### *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).

[1] "Low" was not quantified.

 

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 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.

 