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Fats and Fatty Acids in Human Nutrition

Joint FAO/WHO Expert Consultation

November 10–14, 2008, Geneva, Switzerland

Guest Editors
Barbara Burlingame, Rome
Chizuru Nishida, Geneva
Ricardo Uauy, Santiago de Chile
Robert Weisell, Rome

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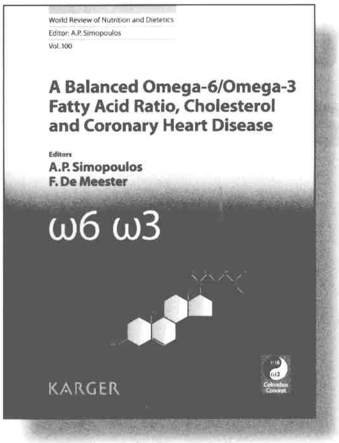
Challenging the role of dietary cholesterol



A Balanced Omega-6/ Omega-3 Fatty Acid Ratio, Cholesterol and Coronary Heart Disease

Editors
Artemis P. Simopoulos
Fabien De Meester

Nutrition, Cardiovascular System, Clinical Nutrition, Metabolism, Evolutionary Biology

For more than half a century, the relationship between dietary factors and coronary heart disease (CHD) has been a major focus of health research. Contrary to the established view, current data suggest that dietary cholesterol is not a primary factor of or causes heart disease – with the possible exception of the genetic forms of familial hypercholesterolemias. For instance, recent clinical trials evaluating the effect of cholesterol-lowering drugs on the development of chronic heart failure, diabetes and stroke have yielded disappointing results. On the other hand, an unbalanced omega-6/omega-3 fatty acid ratio and a cholesterol intake not consistent with the amount during evolution seem to be causal factors in the development of CHD.
A panel of international experts in genetics, nutrition, fatty acid, cholesterol, metabolism and coronary heart disease has contributed to this publication, summarizing and critically discussing for the first time the importance of evolutionary aspects of diet, the omega-6/omega-3 fatty acid ratio and cholesterol intake relative to health and CHD. They also propose measuring blood fatty acids in the population in order to define the risk of CHD and other chronic diseases.
This book will be of interest to physicians (cardiologists, gerontologists, and pediatricians), nutritionists, dieticians, health care providers, scientists in industry and government and policy makers.

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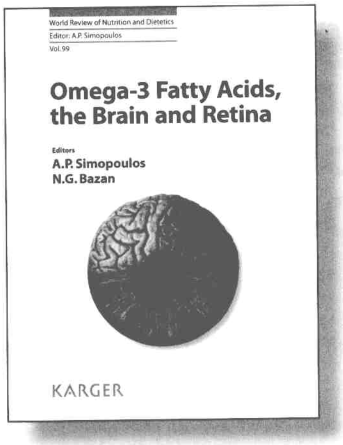
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Dr. Burlingame has nothing to disclose.
Dr. Nishida has nothing to disclose.
Dr. Uauy has served as an ad-hoc technical consultant for Bristol-Myers Squibb and currently for Cadbury; in addition he serves as an ad-hoc consultant for Bimbo Mexico and Kellogg's in advising on scientific awards and prizes related to nutrition.
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Fats and Fatty Acids in Human Nutrition: Introduction

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The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), as technical agencies of the United Nations, are charged with providing science-based guidance on food and nutrition to national governments and the international community. The process used to fulfill this mandate involves systematic reviews of currently available scientific evidence, which often culminate with the convening of joint expert consultations that review the state of scientific knowledge, deliberate the issues, and translate this knowledge into the definition of requirements, the nutritional requirement values and corresponding nutrient-based recommendations. The overall goal of these recommendations is to support the health and nutritional well-being of individuals and populations. Topics recently covered include energy, protein and amino acids, fats and oils, and the majority of vitamin and minerals in addition to carbohydrates with the objective of providing guidance on their requirements and recommended dietary intakes.

The most recently convened expert meeting was the Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition, held in Geneva, Switzerland, November 10–14, 2008. This consultation was the third to be held on the subject of fats in human nutrition, with the first expert consultation on this topic held in 1977 [FAO, 1977] and the second in 1993 [FAO, 1994].

There have been a number of major developments in this field over the past 15 years, with a resulting need to update the 1996 publication and recommendations. A large number of population-based cohort studies and randomized control trials have been conducted that address the impact of fats, and specifically different fatty acids, on health. Knowledge of the role of particular fatty acids in determining health and nutritional well-being and how they exert these effects has expanded dramatically. We now have a better understanding of how they are metabolized in the body, how they control gene transcription and expression, and how they interact with each other. Fats and fatty acids should now be considered as key nutrients that affect both early growth and development, as well as nutrition-related chronic diseases later in life. The benefits and potential risks of these nutrients go well beyond their role as fuels: specific n–3 and n–6 fatty acids are essential nutrients, while others affect the prevalence and severity of cardiovascular disease, diabetes, cancer and age-related functional decline. This makes the process of defining requirements and recommendations more complex, and demonstrates the need to focus on the role of individual fatty acids and how requirements vary with age and physiological status.

With respect to the recommendations of the previous 1993 consultation [FAO, 1994], the 2008 consultation

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placed more emphasis on the role of certain fatty acid categories, an example being the convincing role played by long-chain polyunsaturated fatty acids in neonatal and infant growth and development, as well as a beneficial role in the maintenance of long-term health and prevention of some chronic diseases. There was strong 'convincing' evidence to recommend a reduction in *trans* fatty acids due to an increased risk of developing coronary heart disease and adverse blood lipid changes, including increasing LDL concentrations and adverse changes in the total/LDL-cholesterol ratio.

The timeliness of this expert consultation is also tied to the clear recognition of the increasing global burden of chronic disease. Recent work by the FAO and WHO related to this issue include: the 2002 expert consultation on 'Diet, nutrition and the prevention of chronic diseases' [WHO, 2003], the 2001 expert consultation on 'Human energy requirements' [FAO, 2004] and its companion 2002 expert consultation on 'Protein and amino acid requirements in human nutrition' [WHO, 2007], a 2002 technical workshop on 'Food energy – methods of analysis and conversion factors' [FAO, 2003], and several scientific updates; one by the FAO/WHO in 2006 on carbohydrates in human nutrition [Nishida et al., 2007] and another by the WHO on *trans* fatty acids [Nishida and Uauy, 2009]. To varying degrees, these integrated efforts provide the scientific basis for strategies, programs and projects of the FAO, WHO and their member countries.

During the past 15 years, the changes in diets and lifestyles resulting from industrialization, urbanization, economic development and market globalization have increased rapidly, particularly in developing countries where rapid socioeconomic changes are occurring. Whereas improvements in the standard of living have been observed, this has often been accompanied by unhealthy dietary patterns and insufficient physical activity to maintain energy balance and a healthy weight. The net result has been an increased prevalence of diet-related chronic diseases in all socioeconomic groups; these conditions now represent the main cause of death and disability on a global basis.

Fats are energy dense (37 kJ or 9 kcal per gram), provide the medium for the absorption of fat-soluble vitamins, are a primary contributor to the palatability of food, and are crucial to proper development and survival during the early stages of life – embryonic development and early growth after birth – on through infancy and childhood. Thus, the greater need for fatty acids during pregnancy and lactation is highlighted. The n–3 long-chain fatty acids provide the structural basis for the development of the brain and central nervous system. In contrast, the high intake of saturated fatty acids, and to an even greater extent *trans* fatty acids, substantially contributes to the development of cardiovascular diseases. These claim many lives not only in affluent societies, but now they are also the main cause of adult death in both developed and developing countries.

In preparing and conducting the Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition, the 'Framework for the provision of scientific advice on food safety and nutrition' [FAO/WHO, 2007] was followed. The process of selecting experts began with a call for experts that was posted on both the FAO and WHO websites and publicized through numerous channels, including the network of the UN Standing Committee on Nutrition. All applications were reviewed by a panel of four persons, consisting of one member each from the FAO and WHO and two independent outside experts designated by the FAO and the WHO secretariat. Each application was evaluated carefully, and ranked based on the combination of the applicant's educational background and field of expertise, including scientific publications and membership or participation in scientific panels related to the subject of the expert consultation. After initial evaluation to identify qualified candidates, geographic and gender balance and a mixture of scientific areas of expertise were considered in order to arrive at the final selection. In addition, all experts and authors were required to complete a 'declaration of interest' so as to judge any conflicts of interest or perceived conflict of interest regarding their positions or opinions on certain issues.

Background papers for the expert consultation were commissioned after an extensive review of the topics covered in the two previous expert consultation reports and consultation with experts on additional issues and topics that needed to be addressed given the availability of new scientific evidence. This resulted in 13 background papers, which are published in this special topic issue. In developing the conclusions and recommendations, the authors of the background papers were asked to use the four criteria levels (convincing, probable, possible or insufficient) for the 'strength of evidence' developed and applied by the Joint WHO/FAO Expert Consultation on 'Diet, nutrition and the prevention of chronic disease' [WHO, 2003]. The strength of evidence was also reviewed and evaluated during the expert consultation to arrive at conclusions and recommendations and establish fats and fatty acids requirement levels.

All the background papers were peer reviewed by at least three experts before being forwarded to the expert consultation for review and deliberations. In addition, all the papers were reviewed by the consultation experts before convening. It should be noted, however, that these papers do not represent the final conclusions of the FAO/WHO Expert Consultation.

With the upcoming International Congress on Nutrition in Bangkok in early October 2009, the FAO and WHO decided, in collaboration with S. Karger AG publishers, to produce a special topic issue to the *Annals of Nutrition and Metabolism* that contains all the background papers prepared for the Joint FAO/WHO Expert Consultation on Fats and Fatty Acids, with the hope of providing a useful research and reference source.

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Special acknowledgement and appreciation is expressed to Gina Kennedy who served tirelessly organizing both the preparation of the background papers published in this special topic issue and the expert consultation itself.

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Dr. Burlingame has nothing to disclose. Dr. Nishida has nothing to disclose. Dr. Uauy has served as an ad-hoc technical consultant for Bristol-Myers Squibb and currently for Cadbury; in addition he serves as an ad-hoc consultant for Bimbo Mexico and Kellogg's in advising on scientific awards and prizes related to nutrition. Dr. Weisell has nothing to disclose.

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Fat and Fatty Acid Terminology, Methods of Analysis and Fat Digestion and Metabolism: A Background Review Paper

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Fat and Fatty Acid Terminology

Definition and Classification of Lipids

Fats, oils or lipids consist of a large number of organic compounds including fatty acids, monoacylglycerols, diacylglycerols, triacylglycerols (TGs), phospholipids (PLs), eicosanoids, resolvins, docosanoids, sterols, sterol esters, carotenoids, vitamin A and E, fatty alcohols, hydrocarbons and wax esters. Classically, lipids were defined as substances that are soluble in organic solvents. This is a loose definition and could include a number of non-lipid organic compounds. A novel definition and comprehensive system of classification of lipids were proposed in 2005 [Fahy et al., 2005]. The novel definition is chemically based and defines lipids as small hydrophobic or amphipathic (or amphiphilic) molecules that may originate entirely or in part by condensations of thioesters and/or isoprene units. The proposed lipid classification system enables the cataloguing of lipids and their properties in a way that is compatible with other macromolecular data bases. Using this approach, lipids from biological tissues have been divided into 8 categories, as shown in table 1. Each category contains distinct classes and subclasses of molecules [Fahy et al., 2005].

Table 1. Lipid categories and typical examples. Adapted from Fahy et al. [2005]

Category	Example
Fatty acids	oleic acid
Glycerolipids	triacylglycerol
Glycerophospholipids	phosphatidylcholine
Sphingolipids	sphingosine
Sterol lipids	cholesterol
Prenol lipids	farnesol
Saccharolipids	UDP-3-0-(3-hydroxy-tetradecanoyl)-N-acetylglucosamine
Polyketides	aflatoxin

Lipid Classes

A summary of the 8 lipid classes is presented below. For details see Fahy et al. [2005].

Fatty Acids

These are a diverse group of molecules characterized by a repeating series of methylene groups that impart hydrophobic character. The fatty acyl structure represents the major lipid building block of complex lipids and there-

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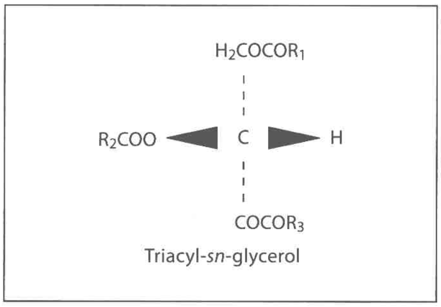

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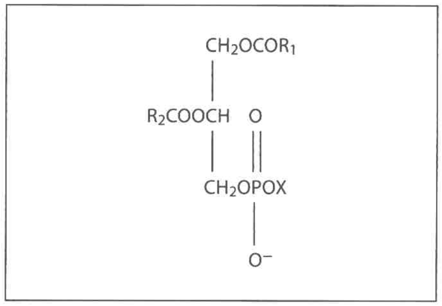

Fig. 1. Chemical structure of triacylglycerol.
Fig. 2. Chemical structure of a phospholipid. X = Choline, ethanolamine, serine, inositol or glycerol.

fore is one of the most fundamental categories of biological lipids. This lipid class includes the various types of fatty acids, eicosanoids, fatty alcohols, fatty aldehydes, fatty esters, fatty amides, fatty nitriles, fatty ethers and hydrocarbons. Many members of this category, especially the eicosanoids derived from n–6 and n–3 polyunsaturated fatty acids (PUFAs), have distinct biological activities.

Glycerolipids

The glycerolipids essentially encompass all glycerol-containing lipids. The most well-known being the fatty acid esters of glycerol (acylglycerols), which includes tri-, di- and mono-acylglycerols. Additional subclasses are represented by glycosylglycerols, which are characterized by the presence of 1 or more sugar residues attached to glycerol via a glycoside linkage. Glycerophospholipids are not included in this category because of their abundance and importance as membrane constituents.

Nutritionally, the TGs are the most predominant group in this category. They comprise the bulk of lipids in seed oils and storage fat in animal tissues. The general chemical structure of a TG is shown in figure 1. Conventionally, the 3 carbon atoms of the glycerol molecule are numbered 1, 2 and 3 from top to bottom. For designation of the stereochemistry of the acylglycerols, the glycerol molecule is drawn in a Fisher projection with the secondary hydroxyl group to the left of the central prochiral carbon atom, and then the carbons are numbered 1, 2 and 3 from top to bottom. Molecules that are stereochemically numbered in this fashion have the prefix '*sn*' immediately preceding the term 'glycerol' in the name of the compound to distinguish them from compounds that are numbered in a conventional fashion.

Differences in the distribution of fatty acids in the 3 positions of the glycerol moiety in dietary TGs have some nutritional implications. In particular, the composition of *sn*–2 is of great importance, since *sn*–2 facilitates the absorption of these fatty acids as 2-monoacyl-*sn*-glycerols and is utilized as such in the re-synthesis of TGs and glycerol PLs that takes place after fat absorption (see 'Absorption of Products of Digestion', below). A considerable amount of data is available in the literature on the stereospecific distribution of fatty acids of common dietary fats [Christie, 2008]. In general in seed oils, the PUFAs are greatly enriched in the *sn*–2 position while saturated fatty acids (SFAs) are concentrated in the *sn*–1 and *sn*–3 positions, and monounsaturated fatty acids (MUFAs) are relatively evenly distributed. In most dietary animal fats, the SFAs are predominantly in the *sn*–1 position, although an appreciable amount of oleic acid (OA) is usually present also. The *sn*–2 position tends to contain mainly PUFAs, especially linoleic acid (LA). In cow's milk, however, all the butyric acid (C4:0) and most of the hexaenoic acid (C6:0) is in the *sn*–3 position, whereas the long-chain SFAs (C14:0, C16:0 and C18:0) are equally distributed at the *sn*–1 and *sn*–2 positions. In human milk, palmitic acid (C16:0) is predominantly in *sn*–2, whereas stearic acid (18:0) is in *sn*–1 position. In marine lipids, SFAs and MUFAs are preferentially in the *sn*–1 and *sn*–3 positions, whereas PUFAs are greatly concentrated in the *sn*–2 position with substantial amounts also being in position *sn*–3.

Glycerophospholipids

These are also referred to as PLs. They are constituents of cell membranes which occur in foods and extracted oils. Glycerophospholipids may be subdivided into distinct classes, based on the nature of the polar head group at the *sn*–3 position of the glycerol backbone in eukaryotes and eubacteria or the *sn*–1 position in the case of archaebacteria. Examples of glycerophospholipids found in biological membranes are phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine. The general structure of glycerophospholipids is shown in figure 2. The X moiety attached to the phosphate includes choline, ethanol amine, serine or hexahydric alcohol. A SFA is usually esterified at position 1 and a PUFA at position 2. The polar group at position 3, which contains phosphorus and the nitrogenous base or sugar molecule, provides the PL molecule with a hydrophilic region. In addition to serving as a primary component of cellular membranes and binding sites for intra- and intercellular proteins, some glycerophospholipids in eukaryotic cells, such as phosphatidic acids, are either precursors of, or are themselves, membrane-derived second messengers. Typically one or both of these hydroxyl groups are acylated with long-chain fatty acids, but there are also alkyl-linked and 1Z-alkenyl-linked (plasmalogen) glycerophospholipids, as well as dialkylether variants in prokaryotes.

Although PLs constitute a small fraction of total dietary fat, they can be important sources of essential fatty acids (EFAs).

Sphingolipids

Sphingolipids are a complex family of compounds that share a common structural feature, a sphingoid base backbone that is synthesized de novo from serine and a long-chain fatty acyl co-enzyme A (CoA), and then converted into ceramides, phosphosphingolipids, glycosphingolipids and other species. The major sphingoid base of mammals is commonly referred to as sphingosine. Ceramides (N-acyl-sphingoid bases) are a major subclass of sphingoid base derivatives with an amide-linked fatty acid. The fatty acids are typically SFAs or MUFAs with chain lengths from 14 to 26 carbon atoms. Ceramides are generally precursors of more complex sphingolipids. The major phosphosphingolipids of mammals are sphingomyelins (ceramide phosphocholines). The glycosphingolipids are a diverse family of molecules composed of 1 or more sugar residues linked via a glycosidic bond to the sphingoid base. Examples of these are the simple and complex glycosphingolipids such as cerebrosides, gangliosides and sulfoglycosphingolipids (sulfatides) that are abundant in myelin.

Sterol Lipids

Sterols are a class of lipids that contain the common steroid nucleus of a fused 4-ring structure with a hydrocarbon side chain and an alcohol group. Structures of some common dietary sterols are illustrated in figure 3. Dietary sterols are found in both animal fats and most vegetable oils and they occur in free form or are esterified to such compounds as fatty acids, glycosides or ferulic acid (oryzanol). Cholesterol is the primary animal fat sterol and is found in vegetable oils in trace amounts. Cholesterol is an important component of membrane lipids. Plant-derived sterols are collectively known as plant sterols or phytosterols. The type and amount of phytosterols vary with the source of oil. The major plant sterols are β-sitosterol, campesterol and stigmasterol, although several others are known to exist [Piironen and Lampi, 2004]. The total sterols (sum of esterified and non-esterified sterols) generally account for 0.2–1.0% of total lipids for most vegetable oils. Refining of vegetable oils removes up to 40% of sterols.

The steroids, which contain the same fused 4-ring core structure, are also included in this sterol lipids category. They have different biological roles from hormones and signaling agents. The C18 steroids include the estrogen family, whereas the C19 steroids comprise the androgens such as testosterone and androsterone. The C21 subclass includes the progestogens as well as the glucocorticoids and mineralocorticoids. The secosteroids, comprising various forms of vitamin D, are characterized by cleavage of the B ring of the core structure. Other examples of sterols are the bile acids and their conjugates, which are synthesized from cholesterol in the liver.

Prenol Lipids

Prenol lipids are synthesized from the 5-carbon precursors isopentenyl diphosphate and dimethylallyl diphosphate that are produced mainly via the mevalonic acid pathway. The simple isoprenoids are linear alcohols, diphosphates, etc., that are formed by the successive addition of C5 units, and are classified according to the number of these terpene units. Structures containing 40 carbons or more are known as polyterpenes. Carotenoids are important simple isoprenoids that function as antioxidants and some carotenoids, but not all (e.g. lycopene), are precursors of vitamin A. Another biologically important class of molecules is exemplified by the quinones and hydroquinones, which contain an isoprenoid tail attached to a quinonoid core of non-isoprenoid origin. Vitamins E and K and the ubiquinones, are examples of this class.

From a nutritional point of view, vitamin E is the most important lipid group in the prenol lipid category. Vitamin E consists of a mixture of lipid-soluble phenols characterized by an aromatic chromanol head and a side chain of 16 carbon atoms. Vitamin E is divided into 2 subclasses: tocopherols and tocotrienols. The tocopherols have a saturated hydrocarbon tail, whereas the tocotrienols are the farnesylated analogues having an unsaturated isoprenoid tail (fig. 4). Both tocopherols and tocotrienols occur as a family of 4 isomers, namely α-, β-, γ- and δ-tocopherol and tocotrienols.

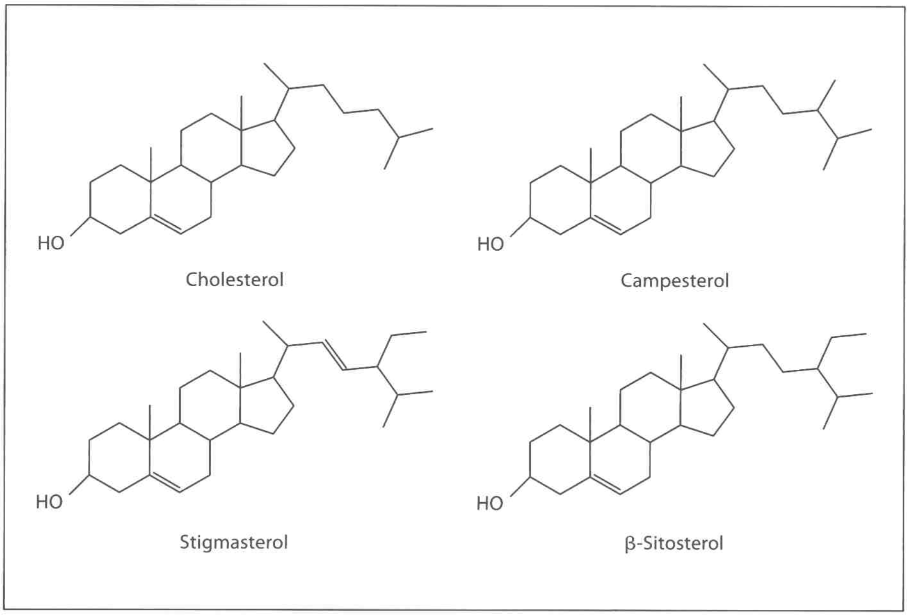

Fig. 3. Chemical structures of some common dietary sterols.

The main well-known biological function of tocopherols is for protection of PUFAs against oxidation. The different tocopherols have different antioxidant activities in vitro and in vivo. In food systems, the antioxidant activity of the tocopherol isomers decreases in the order: $\delta > \gamma > \beta > \alpha$ [Kamal-Eldin and Appelqvist, 1996]. In biological systems, however, the antioxidant activity appears to be limited to α-tocopherol. The other forms of tocopherol do not contribute to vitamin E activity [Institute of Medicine, 2000]. This is because the presence in biological systems of hepatic α-tocopherol transfer protein which selectively binds α-tocopherol, as compared to other vitamin E forms and facilitates its secretion from the liver [Mustacich et al., 2006]. Tocotrienols have weak vitamin E activity but act as antioxidants in foods and provide stability against oxidation.

Evidence from in vitro and animal studies has indicated that the activity of vitamin E is enhanced by the presence of vitamin C [Halpner et al., 1998]. In vitro studies have suggested that synergism between vitamins C and E, in terms of hydrogen exchange between ascorbic acid and tocopheroxyl radicals, leads to recycling of vitamin E [Niki et al., 1984]. However, studies in guinea pigs and humans (healthy women) have not confirmed this interaction to a significant extent [Burton et al., 1990; Jacob et al., 1996].

In addition to its direct antioxidant function, α-tocopherol has specific cellular functions. α-Tocopherol inhibits protein kinase C activity, which is involved in cell proliferation and differentiation in smooth muscle cells, human platelets and monocytes. At physiologically relevant concentrations, α-tocopherol down-regulates the expression of intercellular adhesion molecules, and

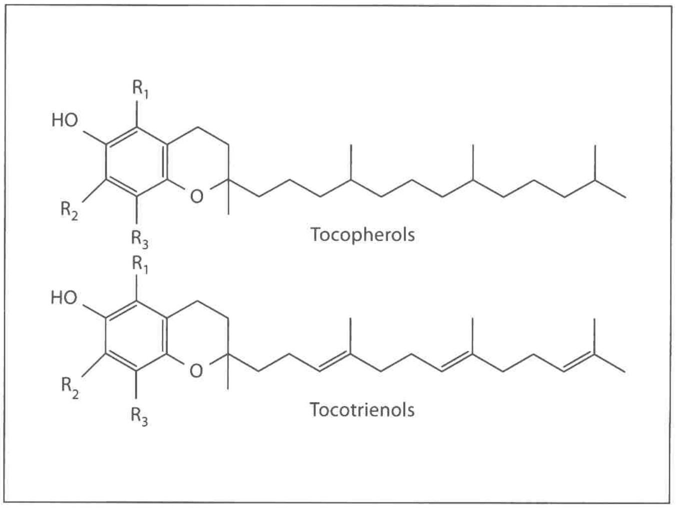

Fig. 4. Vitamin E structures. The methyl groups on the chromanol head determine whether the molecule is α ($R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$), β ($R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$), γ ($R_1 = H$, $R_2 = CH_3$, $R_3 = CH_3$) or δ ($R_1 = H$, $R_2 = H$, $R_3 = CH_3$), while the tail determines whether the molecule is a tocopherol or tocotrienol.